Lipid management in patients with chronic kidney disease

[Au: Title shortened to fit our limit of 90 characters including spaces. OK?]

Charles J Ferro[1], Patrick B Mark[2], Mehmet Kanbay[3], Pantelis Sarafidis[4], Gunnar H. Heine[5], Patrick Rossignol[6], Ziad A. Massy[7], Francesca Mallamaci[8], Jose M Valdivielso[9], Jolanta Malyszko[10], Marianne C. Verhaar[11], Robert Ekart[12], Raymond Vanholder[13], Gerard London[14], Alberto Ortiz[15] and Carmine Zoccali[8]

[1]Department of Renal Medicine, University Hospitals Birmingham, Edgbaston, Birmingham, UK

[2]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[3]Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey

[4]Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece

[5]Saarland University Medical Center, Internal Medicine IV–Nephrology and Hypertension, Homburg, Germany

[6]Centre d'Investigation Clinique Plurithématique Pierre Drouin - INSERM CHU de Nancy, France

[7]Hopital Ambroise Paré, Paris Ile de France Ouest (UVSQ) University, Inserm U1018 Eq 5, Paris, France

[8]CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases, Ospedali Riuniti, 89124 Reggio Calabria, Italy

[9]Vascular and Renal Translational Research Group, UDETMA, REDinREN del ISCIII, IRBLleida, Lleida, Spain

[10]Department of Nephrology, Dialysis Therapy and Internal Medicine, Warsaw Medical University, Warsaw, Poland

[11]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[12]Faculty of Medicine, Maribor University, Maribor, Slovenia

[13]Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Gent, Belgium

[14]Centre Hospitalier F.H. Manhès, France

[15]IIS-Fundacion Jimenez Diaz, School of Medicine, University Autonoma of Madrid, FRIAT and REDINREN, Madrid, Spain

Correspondence: Professor Charles Ferro, Renal Unit, University Hospitals Birmingham, Edgbaston, Birmingham B15 2GW United Kingdom. Tel: +44-121-3715839; Fax: +44-121-3715858; e-mail: charles.ferro@uhb.nhs.uk

Abstract | Glomerular filtration rate is inversely associated with cardiovascular disease independent of conventional risk factors. An increased risk of cardiovascular disease is present even at minor levels of renal impairment and the risk is highest in patients with end-stage renal disease (ESRD) requiring dialysis. Renal dysfunction changes the level, composition, and quality of blood lipids in favour of a more atherogenic profile. Patients with advanced chronic kidney disease or ESRD have a characteristic lipid pattern of hypertriglyceridemia and low HDL-cholesterol levels but normal LDL-cholesterol levels. In the general population, a clear relationship exists between LDL-cholesterol, coronary heart disease and ischaemic stroke. However, in patients with ESRD, LDL-cholesterol seems to show a negative association **[Au: with these outcomes?]** at below average LDL-cholesterol levels and a flat or weakly positive association with mortality at higher LDL-cholesterol levels. Overall, the available data suggest that lowering of LDL-cholesterol is beneficial for prevention of major atherosclerotic events in patients with chronic kidney disease and in kidney transplant recipient but is not beneficial in patients requiring dialysis. **[Au: I've moved the description of the content of your Review to the end of the introduction as per our journal style. To fully reflect the content of your article, please finish off the abstrace with a couple of sentences relating to novel lipid-lowering therapies and the need for reconsideration of the KDIGO guidelines in the light of new data. We have a limit of 200 words for this section.]**

[Au: I have highlighted suggestions for glossary terms throughout your manuscript with a [G]. Please provide succinct, one-sentence definitions for these specialist terms.]

[H1] Introduction

Guidelines regarding the management of lipids in patients with chronic kidney disease (CKD) and especially in those with end-stage renal disease (ESRD) are inconsistent in part owing to important deficiencies in the available data. **[Au: Edit OK?]** In 2013 KDIGO produced a comprehensive clinical practice guideline for lipid management in CKD[1]. **[Au: I suggest that we cite your original Table 1 (now Table 3) in the discussion of KDIGO recommendations at the end of the review so that the table is included next to this discussion in the final layout rather than in the introduction to the Review.]** However, in

contrast to other **[Au: subsequently published?]** guidelines **[Au: Such as?]**, these recommendations are considered by some to be overly conservative and restrictive with respect to patient selection, repeat cholesterol measurements and escalation of lipid-lowering therapy, as well as to possibly encourage a nihilistic approach, particularly in patients who require dialysis[2,3].

To some extent these issues are related to the historical unavailability of low-cost, efficacious and well-tolerated non-statin-based lipid-lowering therapies. However, developments in the understanding of lipid metabolism, increasing evidence supporting the use of novel lipid-lowering therapies, emerging clinical data and the publication of guidelines from learned societies mean that nephrologists and other health professionals may now have to reconsider their attitude towards the use of such therapies in patients with CKD and ESRD.

Here we review the epidemiology, pathogenesis and treatment of dyslipidaemia in patients with CKD and ESRD and in kidney transplant recipients. We discuss the mechanisms of action of novel lipid-lowering agents, evaluate the emerging evidence that supports the use of these therapies and discuss the potential health economic implications of their adoption in clinical practice. **[Au: Edit OK?]** Finally, we reappraise the 2013 KDIGO Clinical Practice Guideline for Lipid Management in the context of the currently available data and more recent lipid management guidelines from other societies. **[Au: Edit of this paragraph OK? I moved some text from the end of your abstract to provide more detail.]**

[H1] Renal function and cardiovascular risk **[Au: We have a limit for main [H1] subheadings of 39 characters including spaces. I have edited the subheadings throughout to fit this limit.]**

A graded inverse relationship exists between estimated glomerular filtration rate (eGFR) and cardiovascular disease, which is independent of age, sex and other conventional cardiovascular risk factors[4,5]. This relationship is present even in the setting of minor renal impairment with most studies showing an increased risk **[Au: of cardiovascular disease?]** at an eGFR <60 ml/min/1.73m^2 and some studies showing an increased number of cardiovascular events even at higher levels of eGFR[4-6]. Moreover, patients with ESRD who require dialysis have an extremely high risk of cardiovascular disease **[Au: ok or should this be cardiovascular events?]**[7]. In Europe, standardized cardiovascular and non-cardiovascular mortality are 8.1 and 8.8 times higher, respectively, in patients on dialysis than in the general population[8]. The mortality of patients with ESRD is twice as high as that of patients with

congestive heart failure and four times that of patients with diabetes mellitus in the absence of CKD[7]. In all relevant studies of patients with early CKD or ESRD published to date, cardiovascular disease is the predominant cause of this increased mortality, accounting for over 50% of all deaths[4,5,7,9].

Kidney transplantation is the treatment of choice for patients with ESRD and is associated with healthcare cost savings, improved quality of life and improved survival[10-13]. Candidates for kidney transplants undergo rigorous cardiovascular investigations before transplantation[14]. However, cardiovascular mortality still accounts for approximately 50% of all deaths in kidney transplant recipients[15].

[H1] Dyslipidaemia in kidney disease **[Au: I have added [H2] subheadings to this section to make it easier to navigate for readers. Please check that you are happy with these headings. We have a limit for [H2] subheadings of 39 characters including spaces.]**
Patients with kidney disease are a very heterogenous population with a wide range of aetiologies of renal damage, levels of renal function and proteinuria, co-morbidities (especially concurrent diabetes), renal replacement modalities and treatments, all of which can affect the levels and properties of circulating lipids[16,17]. **[Au: Edit OK?]** In general, renal dysfunction changes the level, composition, and quality of these lipids in favour of a more atherogenic profile[18-21]. The characteristic lipid pattern in patients with CKD stage 3 or higher consists of hypertriglyceridemia **[G]** , low levels of high-density lipoprotein (HDL) cholesterol and variable levels of low-density lipoprotein (LDL) cholesterol and total cholesterol[18,19,22-25]. However, different CKD stages, modes of dialysis and levels of proteinuria are associated with specific lipid profiles (Table 1). **[Au: Edit OK? We generally avoid referring directly to display items in the text.]**

[H2] Lipid metabolism
Lipid metabolism is complex and involves multiple organs, cells and tissues, including the liver, intestine, plasma, macrophages and vascular endothelium, all of which can be affected by impaired kidney function[19,26] (Figure 1). As fats are hydrophobic and generally insoluble in plasma[26], they are transported within hydrophilic lipoproteins with surface apolipoproteins **[Au: What is the function of apolipoproteins in this context?]**. Hundreds of these proteins **[Au: Are you referring to lipoproteins, apolipoprotiens or both?]** exist[26-28]. Apolipoproteins also act as cofactors and ligands for lipid-processing enzymes.

Dyslipidaemia in patients with CKD occurs as a result of altered metabolism of postprandial lipoproteins and other triglyceride-rich lipoproteins (such as very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL) and LDL), changes in reverse cholesterol transport and lipoprotein structure, post-translational modification of lipoproteins and increased levels of lipoprotein(a) (Lp(a)). **[Au: Edit OK?]**

[H2] Lipoprotein structure

LDL-cholesterol has been a major focus of cardiovascular risk reduction in patients with CKD[16,18,19,22,24,29-32]. However, the levels of LDL-cholesterol and total cholestrol are often within normal limits in these patients[19,24,25,32-36]. Alterations in lipoprotein structure that are associated with CKD, for example an increased predominance of atherogenic small dense LDL particles, might be more important than quantitative changes in cholesterol levels[19,32-36]. The increased pro-atherogenic potential of small dense LDL particles has been linked to their increased capacity to infiltrate the arterial intima and their increased susceptibility to oxidative modification **[Au: compared with which LDL particles?]**[37-39].

[H2] Reverse cholesterol transport

The process of reverse cholesterol transport clears excess cholesterol from the arterial wall through HDL-cholesterol-mediated pathways (Figure 1)[24,26]. This process is negatively affected by CKD at several levels. Expression of the ATP-Binding Cassette (ABC) transporters, ABCA1 and ABCR1, which are key to promoting the efflux of cholesterol from macrophages to lipid-poor HDL precursors,[24,40,41] is reduced in CKD[42]. Activation of the plasma enzyme lecithin-cholesterol acyltransferase (LCAT) by Apolipoprotein-AI (Apo-AI; the major lipoprotein on HDL) to form cholesterol ester from free cholesterol stimulates the maturation of HDL precursors[24,43]. Levels of plasma Apo-A1 and HDL-cholesterol are also significantly reduced in patients with CKD as a consequence of reduced liver synthesis of Apo-A1 and reduced concentration and activity of LCAT[24,43–45].

Cholesterylester transfer protein (CETP) mediates the transfer of cholesterol ester from HDL particles to triglyceride-rich lipoproteins. Low CETP activity leads to increased plasma HDL-cholesterol concentrations and is thought to protect against atheroma **[G]** formation although whether HDL cholesterol levels are a modifiable risk factor remains unclear[24,46,47]. However, CETP activity is increased in patients with CKD[24,48,49]. This impaired HDL-cholesterol metabolism in CKD leads to the accumulation of immature HDL particle precursors with limited anti-oxidative and anti-inflammatory potential [34,50-52]. Renal transplant recipients

often have high levels of HDL-cholesterol but are not protected against atherogenesis, probably as a direct result of the reduced quality of these HDL particles[13,53].

[H2] Hypertriglyceridemia

Plasma triglyceride concentrations are increased in the early stages of CKD with the highest levels in patients on dialysis and in those with nephrotic syndrome [34,54]. The ratio of triglycerides to cholesterol in LDL and HDL particles is also increased in patients with CKD[24]. Hypertriglyceridemia **[G]** in CKD results from delayed catabolism of triglyceride rich lipoproteins, including VLDL particles and chylomicron **[G]** remnants, coupled to reduced LCAT activity[34,43]. Lipoprotein lipase (LPL) expression is reduced and the levels of Apolipoprotein C-III (Apo C-III), a competitive inhibitor of LPL, are increased in CKD[24,55]. LPL hydrolyses triglycerides transported within VLDL particles and chylomicrons[56,57]. Clearance of VLDL particles from the circulation, and their transformation into IDL particles, are also impaired in CKD because of reduced expression of VLDL receptors in adipocytes and myocytes [25,58-60]. Glucose loading in patients on peritoneal dialysis[61] and recurrent heparinisation in those on haemodialysis are also thought to contribute **[Au: to this reduced expression?]**[62]. Switching from conventional thrice-weekly 4-hour haemodialysis sessions to more intensive regimens such as nocturnal haemodialysis has been reported to lower triglyceride concentrations and increase HDL-cholesterol levels[63].

Attention has focused on alterations of triglyceride-rich lipoproteins as predictors of cardiovascular disease[64]. In the general population, Mendelian randomization analyses support the hypothesis of a causal association between triglyceride and lipoprotein abnormalities, including smaller and denser LDL and HDL particles and cardiovascular disease[64,65]. Patients with an eGFR <60 ml/min/1.73m^2 have a highly-prevalent dyslipidemic phenotype consisting of increased levels of triglyceride-rich lipoproteins that is strongly associated with a high subclinical atherosclerosis burden[66,67] and has also been shown to be associated with increased risk of coronary heart disease[68]. Hypertriglyceridaemia is also a strong **[Au: risk?]** factor for cardiovascular events and mortality in patients on haemodialysis with abdominal obesity[69].

[H2] Lipoprotein(a)

Lp(a) is a unique lipoprotein that consists of a central LDL-like core containing a single molecule of Apoprotein-B (ApoB) linked by a disulphide bridge to Apoprotein(a) [31,70,71]. Lp(a) binds to the extracellular matrix and is highly atherogenic[31]. Plasma Lp(a) levels are

primarily genetically determined by Lp(a) gene variants and are thought to be causally associated with high cardiovascular risk based on epidemiologic, genetic association and Mendelian randomization studies[31,70,72-76]. Interestingly this association seems to become less important once coronary artery disease is established[77]. Elevated Lp(a) levels are also independently associated with risk of myocardial infarction and death in patients with CKD[78].

The metabolic pathways of Lp(a) production and clearance are not well understood[70]. However, plasma Lp(a) levels seem to increase early in CKD owing to decreased clearance[79] and are increased up to 4-fold in patients with nephrotic syndrome [80,81]. Lp(a) is thought to competitively inhibit fibrinolysis **[G]** and thus predispose to thrombosis and may also directly promote atherosclerosis[70]. The 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias recommend measuring of ApoB as an complementary risk marker, especially in patients with high triglyceride levels, and measuring of Lp(a) levels in selected patients at high risk of cardiovascular disease, in patients with premature cardiovascular disease, and for reclassification in patients with borderline cardiovascular risk[79].

[H2] Oxidative stress

Oxidative stress increases as renal function declines[82], leading to increased oxidation of circulating lipids[19]. The resulting oxidation products such as oxysterols[83,84], malondialdehyde [85,86], and oxidized HDL and LDL particles[87,88] have increased atherogenic potential. Studies of the lipidomic profile in the CKD population show a reduction in phosphatidylcholines, sulfatides and ceramides in LDL particles, as well as an increase in N-acyltaurines [89]. These alterations may contribute to the pro-atherogenic potential of lipoproteins in CKD. Other qualitative abnormalities such as glycosylation and carbamylation have been reported in patients with CKD[90]. HDL particles in adult and paediatric patients with CKD are modified by retained symmetric dimethylarginine promoting endothelial dysfunction and atherogenesis[91].

[H2] Nephrotic syndrome

Independent of alterations in GFR, increasing levels of albuminuria are associated with dysregulation of lipid metabolism and dyslipidaemia,which is exemplified in patients with nephrotic syndrome[80,81,92]. These patients typically have marked hypercholesterolaemia, hypertriglyceridaemia and low to normal HDL-cholesterol levels. These changes are mediated by changes in the expression and activity of key protein mediators of lipid metabolism, including decreased LPL activity and decreased expression of the LDL-receptor

(LDL-R) [80,81,92], which in part relate to the insulin resistant state that is observed in these patients. Profound alterations in the structure and function of HDL particles are also present **[Au: in patients with nephrotic syndrome?]**[81]. Increases in proprotein convertase subtilisin–kexin type 9 (PCSK9) are also thought to contribute to the hypercholesterolaemia that is associated with nephrotic syndrome[80,93]. Plasma PCSK9 concentrations do not increase with decreasing GFR **[Au: Please explain why this finding is important.]**[94].

[H2] Immunosuppressive medication

Kidney transplant recipients and patients with autoimmune or inflammatory conditions, which can be a cause of renal damage or an associated comorbidity, require treatment with immunosuppressive medication, which substantially alter lipid profiles[95]. Calcineurin inhibitors, particularly ciclosporin, increase LDL-cholesterol levels by a number of mechanisms, including reduced binding to the LDL-R, decreased bile acid synthesis and the promotion of glucose intolerance[96,97]. Although ciclosporin and tacrolimus seem to have similar actions on lipid metabolism and glucose intolerance, the use of ciclosporin is consistently associated with increased levels of LDL-cholesterol and Apo(B)[98-100]. mTOR inhibitors have anti-atherogenic effects but raise LDL-cholesterol levels at least as much as or even more than calcineurin inhibitors by a number of potential mechanisms including inhibition of LPL and increased lipoprotein synthesis **[Au: Edit OK?]**[95,101-103]. In addition, corticosteroids induce insulin resistance and dose-dependently increase concentrations of circulating cholesterol and triglycerides[95]. The effects of these drugs on dyslipidemia is additive to that of other immune-suppressive agents.

[H1] Lipids and cardiovascular disease

In the general population, a clear linear relationship exists between plasma cholesterol concentration and the risk of coronary heart disease and ischaemic stroke. For every 1 mmol/L (40 mg/dL) increase in LDL-cholesterol, the risk of coronary heart disease increases by 40%[104]. However, in patients with ESRD on dialysis, LDL-cholesterol has a negative association with all-cause mortality at below average LDL-cholesterol levels and a flat or weakly positive association at higher levels[105,106]. **[Au: Edit OK?]** This relationship, which holds for patients on haemodialysis or peritoneal dialysis and when cardiovascular death is considered as a separate outcome[106], is often referred to as “reverse epidemiology”, “reverse causality” or “the risk factor paradox”. That is, CKD or an associated co-morbidity causes both reduced LDL-cholesterol levels and an increased risk of death, thus creating a potentially deceptive association between low LDL-cholesterol levels and mortality[107,108]. However, an analysis of

the Study of Heart and Renal Protection (SHARP) found a weak linear relationship between LDL-cholesterol and the risk of major vascular events (HR 1.14, 95% CI 1.06-1.22 per 0.6 mmol/L increase in LDL-cholesterol) in 9,270 patients with moderate to advanced CKD, including 3,015 patients on dialysis[109]. **[Au: Please clarify how this finding supports or does not support the reverse causality hypothesis as this is not currently clear.]**

Another possible or complimentary explanation **[Au: "for the inverse relationship between LDL-cholesterol levels and all-cause mortality in patients with ESRD"?]** is that CKD results in a unique cardiovascular phenotype with fewer deaths due to atherosclerotic processes but more deaths owing to heart failure and sudden cardiac death[110-112]. The pathophysiology of these conditions seems to be associated with disturbances of calcium and phosphate metabolism, hypertension, arrhythmogenic electrolyte disorders, hypervolaemia, uraemic toxins and anaemia[113-115]. A specific pattern of myocardial fibrosis that is found in patients with CKD and ESRD known as cardiomyopathy of CKD or uraemic cardiomyopathy is thought to form the pathophysiological basis for this phenotype, which is a powerful predictor of cardiovascular mortality in these patients[115-117].

Increased HDL-cholesterol levels are associated with decreased cardiovascular risk in the general population[118-120]. However, RCTs in this population have not shown significant benefits of increasing HDL-cholesterol levels with non-statin medications, including niacin[121-124]. Low levels of HDL-cholesterol are common among patients with CKD and ESRD[125-127] but they do not seem to be associated with increased cardiovascular risk after adjustment for traditional risk factors[128,129]. Some studies show a J-curve association with increased mortality among patients with ESRD who have very low or very high HDL-cholesterol levels[130-132]. These data further support the importance of renal-function-induced changes in the composition and quality of lipoproteins.

In the general population, hypertriglyceridaemia is an independent cardiovascular risk factor although the association is far weaker than for hypercholesterolaemia[133]. Elevated triglyceride levels are common in patients with CKD and ESRD, especially in those with insulin resistance and diabetes mellitus, and in those who are receiving peritoneal dialysis[134-137].

[H1] Statin therapy

Beneficial effects of lowering LDL-cholesterol levels using HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme) reductase inhibitors, commonly known as statins, are well established in patients without renal dysfunction. Their safety and efficacy has been demonstrated in the setting of secondary prevention following an atherosclerotic cardiovascular event in several adequately powered RCTs[138,139], and as primary prevention in patients at increased cardiovascular risk such as those with diabetes[140,141].

The overwhelming nature and magnitude of benefit of statin therapy in high-risk populations has also been demonstrated in a number of meta-analyses from the Cholesterol Treatment Trialists (CTT) collaboration [142-145]. Statins might also be beneficial as primary therapy to prevent cardiovascular disease in lower risk populations[145] such as in men with hypercholesterolaemia[146] or in men and women with high levels of high-sensitivity C-Reactive protein (hsCRP; a marker of inflammation) in the absence of hyperlipidaemia [147]. To date, all of the large randomized controlled studies (RCTs) that have investigated the efficacy of lipid-lowering therapy for the prevention of cardiovascular events in patients with kidney disease have been performed using statins.

[H2] Randomized controlled trials

Many of the early RCTs of statin therapy **[Au: of statin therapy?]** did not focus on renal dysfunction as a cardiovascular risk factor. However, the Pravastatin Pooling Project, which combined the results of three placebo-controlled pravastatin trials, demonstrated that reduced kidney function (eGFR 30-59 ml/min/1.73m^2) was a predictor of cardiovascular events and that lipid lowering was associated with a reduction in the rate of these events in patients with reduced kidney function **[Au: Edit OK?]**[148]. Similar results were seen in patients with reduced kidney function (defined as eGFR <60 ml/min/1.73m^2) in the JUPITER[149] and Treating to New Targets (TNT) trials[150].

[H3] Kidney transplant recipients. The first large RCT of statin therapy for the prevention of cardiovascular events in kidney transplant recipient was the Assessment of Lescol in Renal Transplantation (ALERT) study, which included 2,102 kidney transplant recipients receiving ciclosporin-based immunosuppression with stable graft function and total cholesterol levels of 4.0-9.0 mmol/L (155–350 mg/dL) or 4.0-7.0 mmol/L (155–270 mg/dL) if they had previously experienced a myocardial infarction[151]. Patients were randomly assigned to 40 mg fluvastatin or placebo and followed for a mean of 5.1 years. LDL-cholesterol was 1.0 mmol/L (40 mg/dL) lower in the statin group than in the placebo group following the intervention **[Au: at what**

follow-up?]. Although intervention with fluvastatin failed to reduce the incidence of the combined primary end point of major cardiac events (defined as cardiac death, non-fatal myocardial infarction or coronary intervention), this lipid-lowering therapy was associated with a significant reduction in non-fatal myocardial infarction and cardiac deaths[151]. However, the fairly low number of patients and the lack of a run-in period limited the power of ALERT to detect a difference in outcomes over this time period.

In a complex extension study, all of the ALERT participants were offered open-label, longer-term high dose (80 mg) fluvastatin and followed for a total of 6.7 years[152]. During this period, the benefits of random assignment to the fluvastatin group in the initial study in terms of non-fatal myocardial infarction and cardiac death were sustained **[Au: Edit OK?]**. Therefore, the overall conclusion was that statins seem to be safe and efficacious at reducing atherosclerotic cardiovascular events in renal transplant recipients. Some discrepancies were observed in the magnitude of benefit in kidney transplant recipients compared to non-ESRD populations **[Au: in which studies?]**, mainly driven by lack of effect on coronary artery revascularization. **[Au: Please provide a bit more detail on these discrepancies. Was the magnitude of benefit in transplant recipients not as great as in the general population?]**

[H3] Patients with CKD or ESRD. Two large RCTs in patients on dialysis, the Die Deutsche Diabetes Dialyse Studie (4D)[154] and A Study to Evaluate the Use of Rosuvastatin **[Au: Changed from atorvastatin. OK?]** in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)[153], showed no benefit of statin therapy in patients with ESRD. In the 4D study, 1,255 patients with diabetes who had been on haemodialysis for <2 years (of whom 29% had prior cardiovascular disease) were randomly assigned to atorvastatin 20 mg or placebo, with those on a statin undergoing a washout period with placebo for 4 weeks[154]. In the intervention group, LDL-cholesterol levels were reduced from median of 3.13 mmol/L (121 mg/dL) by a mean of 1.27 mmol/L (49 mg/dL) **[Au: at what time point?]**. Despite this reduction, no significant reduction was observed in the incidence of the combined outcome of major cardiovascular events (**[Au: death from cardiac causes, nonfatal myocardial infarction, and stroke?]**) with atorvastatin compared with placebo over a median of 4 years of follow up (HR 0.92, 95% CI 0.77-1.10). However, atorvastatin therapy did reduce the rate of all cardiac events combined compared with placebo (RR 0.82 95% CI 0.68-0.99).

In AURORA, 2,776 patients who had been treated with haemodialysis for at least 3 months and were not receiving statin therapy were randomly assigned to rosuvastatin 10 mg daily or placebo[153]. Nearly 40% of patients enrolled in AURORA had known cardiovascular disease of whom 10% **[Au:OK?]** had a prior myocardial infarction. The fact that these patients were not on statins at recruitment might illustrate the undertreatment of patients **[Au: "with ESRD"?]** even for secondary prevention **[Au: "of cardiovascular disease"?]**. In contrast to the 4D study, 74% of the AURORA participants were diabetic; however only patients over the age of 50 years were recruited whereas the 4D participants were aged over 18 years. Although LDL-cholesterol levels **[Au: "in the rosuvastatin group"?]** fell by 43% from a mean baseline of 2.6 mmol/L (100 mg/dL), and this reduction was accompanied by a significant decrease in C-reactive protein levels, no significant reduction was observed in the incidence of major cardiac events with rosuvastatin compared to placebo after a median follow up of 3.8 years (HR 0.96 95% CI 0.84-1.11). However, the combined primary end point in AURORA was not specific and included non-atherosclerotic events.

Importantly, patients were not selected on the basis of hypercholesterolaemia in any of these studies **[Au: Are you referring to ALERT, 4D and AURORA or just 4D and AURORA here?]**. Although patients with an LDL-cholesterol level >4.9 mmol/L (190 mg/dL) were excluded from the 4D trial[154], atorvastatin therapy significantly reduced the risk of fatal and non-fatal cardiac events in participants with a pre-treatment LDL-cholesterol level >3.76 mmol/L (>145 mg/dl)[155]. However, this type of subanalysis should be interpreted with caution. **[Au: Why?]**

The double-blind, randomized Study of Heart and Renal Protection (SHARP) tested the effect of lipid lowering with simvastatin plus ezetimibe for primary prevention of atherosclerotic vascular events in 9,270 patients with CKD[156]. At enrollment, 6,247 of these patients did not require dialysis and had a serum creatinine level greater than 150 μmol/L (1.7 mg/dL) for men or greater than 130 μmol/L (1.5 mg/dL) for women; the remaining 3,023 patients were on dialysis[156]. Of note, about 30% of the study population had stage 4 CKD and 13% were already at Stage 5 CKD but not on dialysis; thus, 75% of the study population had CKD Stage 4 or 5.

On enrolment, the SHARP participants were initially randomly assigned to simvastatin plus ezetimibe, simvastatin alone and placebo groups. After 1 year, those who were initially allocated to simvastatin alone were randomly re-assigned to receive either simvastatin plus ezetimibe or placebo. Lipid lowering with simvastatin 20 mg combined with ezetimibe 10 mg

led to a mean difference in LDL-cholesterol levels of 0·85 mmol/L (33 mg/dL) compared to placebo. After an average of 4.9 years of follow up, a significant reduction (HR 0.83 95% CI 0.74-0.94) was observed in major atherosclerotic events **[Au: in the simvastatin plus ezetimibe group?]**.

The cardiovascular events in SHARP were more tightly defined than in 4D or AURORA, specifically focusing on thrombo-occlusive disease that would be modifiable with lipid-lowering therapy. Thus the primary outcome was a composite of major atherosclerotic events (coronary death, myocardial infarction, non-haemorrhagic stroke or any revascularization). The effect of treatment **[Au: do you mean lipid lowering?]** was not associated with a significant reduction in these events when only patients who were already on dialysis at enrolment were considered (HR 0.90 95% CI 0.75-1.08). However, SHARP was not powered to detect a benefit in this patient group. After weighting for subgroup-specific reductions in LDL-cholesterol levels, the effects on outcomes in patients on dialysis did not differ from those in patients with non-dialysed CKD (χ^2=1.34; P=0.25). The SHARP study clearly demonstrates a benefit of lowering LDL-cholesterol levels in patients with CKD not requiring dialysis, which is in keeping with the association of these levels with cardiovascular disease in this population[109,157]. Notably, a post hoc analysis of the SHARP data showed that lowering of LDL-cholesterol was not associated with any delay in progression of CKD[158]. This finding is in line with the results of a subsequent meta-analysis[159].

Despite the differences **[Au: in study populations, interventions and outcomes?]** between the 4D, AURORA and SHARP studies, the apparent lack of efficacy of statins for prevention of cardiovascular events in patients on dialysis was remarkably similar. Several potential explanations for this failure exist. First, LDL-cholesterol is not associated with cardiovascular disease in patients on dialysis. However, such a lack of association seems unlikely given the well-established direct causal relationship between LDL-cholesterol and atheroma[143,145]. Second, cardiovascular events in patients on dialysis are proportionally increased due to non-atheromatous processes such as sudden death and heart failure, which would not necessarily be directly improved by lowering of LDL-cholesterol levels[110,111]. Third, all three studies had relatively small numbers of patients on dialysis compared with other studies of lipid lowering therapies (for example the Scandinavian Simvastatin Survival Study (n = 4,444)[138] and the West of Scotland Coronary Prevention Study (n = 6,595)[146]) and could therefore have been underpowered to detect a modest effect.

[H3] Adverse effects. **[Au: I've moved this discussion from the health economics section as I think it is more logical to include it in the discussin of statin therapy. OK?]** In the very large RCTs conducted to date, the only serious adverse events that have been reported with long-term statin treatment are myopathy (defined as muscle pain and/or weakness in conjunction with significantly raised serum creatine kinase levels), new onset diabetes mellitus and possibly haemorrhagic stroke **[Au: Please reference this statement.]**. Treating 10,000 patients for 5 years with an effective statin (for example atorvastatin 40 mg) would cause five cases of myopathy, with one case progressing to full-blown rhabdomyolysis if the statin was not discontinued, 50-100 cases of muscle pain and weakness that do not meet the criteria for myopathy, 50-100 cases of diabetes mellitus and 5-10 haemorrhagic strokes. **[Au: Please reference this statement.]** The findings of large placebo-controlled RCTs suggest that most of these adverse effects are not directly attributable to the statin treatment[144]. However, controversy persists regarding how well data on adverse effects have been collected in these RCTs[260].

[H2] Meta-analyses

Meta-analyses have shown that the proportional reduction in LDL-cholesterol levels achieved during statin trials in the general population is directly associated with the proportional reduction in risk of major vascular events[142]. In these studies, a 1 mmol/L reduction in LDL-cholesterol is associated with a 22-23% reduction in these events[142]. Although observational data have important limitations, especially in regards to confounding and bias[144], this reduction is approximately half that predicted from the observational relationship (40% would be expected)[104]. This finding is perhaps not particularly surprising. In most of the **[Au: statin?]** trials patients were treated for around 5 years whereas exposure to LDL-cholesterol in epidemiological studies lasts a lifetime. However, the relationship seems to be modified in patients with CKD suggesting that the worse the renal function, the lower the cardiovascular risk reduction per reduction in LDL-cholesterol levels[112,160] with no risk reduction being demonstrable in patients on dialysis[112]. In general, statins tend to increase circulating levels of Lp(a) and these may contribute to residual cardiovascular risk **[Au: despite lowering of LDL cholesterol levels?]**[161]. As discussed above, circulating concentrations of Lp(a) increase with declining renal function and are highest in patients on dialysis[162]. Whether this finding explains the reduced cardiovascular benefit of LDL-lowering in patients with CKD compared with the general population remains to be determined[162]. **[Au: Edit OK? Is this what you meant?]**

A number of meta-analyses have pooled data from trials in patients with varying degrees of CKD and ESRD to study the effect of lipid lowering with statins and/or lowering of LDL-cholesterol using ezetimibe in these populations **[Au: Refs 164-169?]**. The consistent finding of the individual trials is that lowering of LDL-cholesterol is beneficial for prevention of major atherosclerotic events in patients not requiring dialysis (including kidney transplant recipients), whereas lipid lowering has no obvious benefit in patients on dialysis. **[Au: Edit OK?]** However, the findings of the meta-analyses are somewhat conflicting[164-169]. **[Au:OK?]**

The most comprehensive of these meta-analyses, which was conducted by the CTT collaboration, analysed data from 28 trials of statin-based therapy in patients with various degrees of renal impairment and included readjudication of all deaths in the AURORA trial to align with atherosclerotic end-points in the trials conducted in patients on dialysis[112]. This meta-analysis demonstrated that as eGFR declines there is a trend towards smaller relative risk reductions for major coronary events and strokes with stain therapy, even after adjusting for smaller reductions in LDL-cholesterol levels in patients with more severe CKD. In particular, there was little evidence that statin-based therapy reduced cardiovascular events in patients who were already on dialysis[112]. However, despite the reduced relative risk benefit of statin-based cholesterol lowering in ESRD, an absolute benefit may persist as the total number of atherosclerotic events in this population is extremely high, especially in high-risk patients such as those with concomitant diabetes mellitus[3,112]. Indeed, a sub-analysis of the 4D study showed that atorvastatin treatment significantly lowered the risk of fatal and nonfatal cardiac events in patients with type 2 diabetes on haemodialysis with pre-treatment LDL-cholesterol levels >3.76 mmol/L (>145 mg/dL)[155]. However, as always, the results of secondary analyses should be interpreted with caution.

[H2] Anti-inflammatory effects

Inflammation has been implicated in the pathophysiology of cardiovascular disease in the general population and in patients with CKD **[Au: or ESRD?]**[170,171]. A chronic inflammatory state is observed in these patients owing to factors including decreased clearance of pro-inflammatory cytokines, increased oxidative stress, acidosis, infections and the dialysis procedure[177-180]. Therefore, targeting inflammation, either directly or indirectly might improve outcomes independently of lipid-lowering in patients with CKD or ESRD. **[Au: I suggest that you cut the discussion of the CANTOS study as it does not fit the scope of lipid-lowering therapies in CKD/ESRD or the subheading of anti-inflammatory effects of statins.]**

Several lines of evidence support an anti-inflammatory action of statins **[Au:OK?]**[172]. Moreover, the JUPITER trial showed that potent statin therapy reduced the risk of major cardiovascular events by 44% in patients with elevated levels of hsCRP[173]. Intriguingly, this reduction in cardiovascular risk was associated with the **[Au: reduction in?]** level of hsCRP but not with that of LDL-cholesterol. **[Au: Please can you check if this is correct. The abstract says that a reduction in LDL cholesterol to less than 1.8 mmol was associated with a 55% reduction in vascular events.]** Similar reductions in cardiovascular risk were found in a secondary analysis of the 3,267 JUPITER participants who had an eGFR <60 ml/min/1.73m^2.[149] However, in this subgroup similar reductions were observed in the levels of hsCRP and LDL-cholesterol. **[Au: Please clarify the point that you are making here. Do you mean that statin therapy resulted in similar reductions in hsCRP and LDL-C or that reductions in hsCRP and LDL-C were similarly associated with reducions in cardiovascular events?]** Of note, patients with a creatinine level greater than 177 μmol/L (greater than 2 mg/dL) were excluded from the JUPITER trial.

A sub-analysis of the SHARP trial showed that although higher baseline hsCRP levels were associated with an increased risk of major cardiovascular events, the reduction in cardiovascular risk in those who received combination therapy with simvastatin and ezetimibe was similar irrespective of baseline hsCRP[109]. **[Au: Edit OK?]** Although the results of subanalyses should be interpreted with caution, this finding suggests that the simvastatin and ezetimibe combination reduces cardiovascular risk independently of the presence of inflammation.

[H1] Fibrates

RCTs have shown that lowering triglyceride levels with fibrate monotherapy decreases cardiovascular risk in the general population, although this benefit may be limited to individuals with very high triglyceride and very low HDL-cholesterol levels[181-184]. However, the use of fibrates, although possibly not gemfibrozil[185], to lower triglyceride levels may increase creatinine levels, especially in patients with eGFR <30 ml/min/1.73m^2 [184,186,187], by mechanisms that are not fully elucidated[184,188,189]. Currently very little evidence exists to recommend the use of fibrates in patients with CKD unless triglyceride levels are very high (>1,000 mg/dL; 11.3 mmol/L) in which case these therapies should be used judiciously and dose adjusted for renal function[1].

[H1] Bile acid sequesterants

[Au: What is the rationale for using bile acid sequeserants or omega-3 oil in patients wih CV disease or CKD? What is their effect on lipids?] Although bile acid sequestrants (cholestyramine, colestipol, colesevelam) are currently recommended as second-line options in patients with atherosclerotic cardiovascular disease [79,190] a 2018 meta-analysis failed to identify any RCTs **[Au: showing a benefit of these agents?]** with more than 500 patients and greater than 1 year follow-up [191]. Currently very little evidence exists to support the use of bile acid sequestrants or prescription omega-3 oil in patients with CKD or ESRD.

[H1] Emerging lipid-lowering therapies

Treatment of dyslipidaemia with the most widely used lipid-lowering drugs provides a significant reduction in cardiovascular risk. However, a significant proportion of **[Au: treated?]** patients will continue to have cardiovascular events[31,192]. Several novel therapies for the treatment of dyslipidaemias and their associated risks are being developed. These therapies include agents that target major mediators of the clearance and secretion of atherogenic proteins (Table 2). **[Au: ATP citrate lyase inhibitors, acetylcoenzyme A carboxylase inhibitors and diacylglycerol acyltransferase 1 inhibitors are included in table 2 but do not seem to be discussed in the main text. For completeness, please also discuss these agents if appropriate.]**

[H2] PCSK9 inhibitors

[Au: I've rearranged text in this paragraph to improve flow.] Proprotein convertase subtilisin–kexin type 9 (PCSK9) is a secreted serine protease that binds to the extracellular domain of the hepatocyte LDL-receptor and promotes its lysosomal degradation. This receptor degradation reduces LDL particle uptake and leads to increased concentrations of **[Au: circulating?]** LDL-cholesterol (Figure 2)[199,200]. In 2003, gain-of-function mutations in the gene encoding PCSK9[193] were reported to cause autosomal dominant hypercholesterolemia[194]. Subsequently, loss-of-function mutations in PCSK9 were discovered to reduce LDL-cholesterol levels by 15-28% and the risk of coronary heart disease by 47–88%[195-198].

Monoclonal antibodies that act as PCSK9 inhibitors sequester PCSK9 and thereby prevent LDL-receptor catabolism so lead to an increase in LDL-receptor density on hepatocytes[17,201]. The efficacy of one such antibody, alirocumab, has been investigated in the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Recently

Experienced an Acute Coronary Syndrome (ODYSSEY) clinical trial program, which includes approximately 23,500 patients worldwide. **[Au: Please reference this statement.]** Overall, these trials showed that alirocumab therapy reduced LDL-cholesterol levels by 36%-61% after a minimum of 24 weeks of treatment **[Au: Please reference the original paper from the ODYSSEY program in which this data was published.]**. Alirocumab also consistently reduced concentrations of total cholesterol, ApoB, non-HDL-cholesterol, and Lp(a) independently of statin treatment and of additional ezetimibe use in heterozygous familial hypercholesterolaemia (HeFH) and non-FH populations[202]. A post hoc analysis of the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study showed a 52% reduction in major cardiovascular events after alirocumab treatment in patients with HeFH and high cardiovascular risk already on the highest tolerated dose of statins [204].

An analysis that pooled data from 8 phase 3 ODYSSEY trials of double-blind treatment with alirocumab for 24-104 weeks included 4,629 patients with hypercholesterolaemia of whom 467 had CKD stage 3[203]. Among the patients with CKD, 315 were randomly assigned to alirocumab and 99% were already receiving a statin. The reduction in LDL-cholesterol levels at week 24 in patients with CKD treated with alirocumab ranged from 46.1% to 62.2% with an efficacy and safety profile comparable to that of patients with normal renal function (eGFR >60 ml/min/1.73m^2).

The ODYSSEY OUTCOMES trial included 18,924 participants who had experienced an acute coronary event 1-12 months before enrolment[205]. Following a run-in phase of 2-16 weeks on high intensity statin therapy, these participants were randomly assigned to fortnightly alicorumab treatment or placebo groups. The alicorumab therapy was titrated to keep LDL-cholesterol levels between 0.65 mmol/l and 1.3 mmol/L (25-50 mg/dL). In this trial, alicorumab therapy resulted in a significant reduction in the primary outcome of major cardiac events (HR 0.85; 95% CI 0.78-0.93; P=0.0003) [205]. **[Au: Were patients with CKD included in this trial? If so is here any data on outcomes in this population?]**

The efficacy of another PCSK9 inhibitor, evolocumab, is being assessed in the Program to Reduce LDL-cholesterol and Cardiovascular Outcomes Following Inhibition of PCSK9 in Different Populations (PROFICIO)[206-210]. This program of 14 phase III clinical trials aims to recruit approximately 30,000 patients. So far, studies have ranged from from 10 to 52 weeks

in duration and have included patients treated either with evolocumab monotherapy or with evolocumab in combination with a statin or ezetimibe **[Au: Is in combination with correct?]**. Very significant reductions in LDL-cholesterol levels have been reported, ranging from 49%-65% ,with substantial reductions in the levels of non-HDL-cholesterol, ApoB and Lp(a) and modest effects on triglycerides and HDL-cholesterol. In addition, coronary atheroma regression with evolocumab compared with placebo (-0.95% versus +0.05%) has been reported in a double-blind, placebo-controlled trial in 968 patients with proven coronary atheroma on angiography that used serial intravascular ultrasound to assess atheroma volume[211]. A greater proportion of patients in the evolocumab group than in the placebo group also had plaque regression in this trial (64.3% versus 47.3%)[211].

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, included 27,550 patients with known atherosclerotic vascular disease (previous myocardial infarction, non-haemorrhagic stroke or symptomatic peripheral vascular disease), LDL-cholesterol greater than 1.8 mmol/L (>70 mg/dL) or non-HDL-cholesterol greater than 2.6 mmol/L (>100 mg/dL) already on optimized statin therapy [212]. This study reported a significant reduction in the primary outcome (composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization) with evolocumab therapy (9.8%) compared with placebo (11.3%) (HR 0.85 95% CI 0.79-0.92) [212]. Although patients with an eGFR >20 ml/min/1.73m^2 were eligible for inclusion in FOURIER[213], no information on the number and of patients with CKD who were enrolled and the outcomes in this population is currently available.

The safety and efficacy of another monoclonal antibody, bococizumab, in patients at high cardiovascular risk was investigated in the Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) 1 and SPIRE 2[214]. **[Au: What were the findings of these studies?]** However, further clinical development of this agent has been stopped because of an unexpected decrease in LDL-cholesterol lowering over time, high levels of immunogenicity and high rates of injection-site reactions[31].

Unlike therapeutic antibodies which bind to and inhibit their target protein, treatment with short interfering RNAs (siRNAs) results in the destruction of the target messenger RNA and reduces the production of the protein[215]. Inclisiran (ALN-PCSSC) is a fully chemically modified, siRNA conjugated to triantennary N-acetylgalactosamine that inhibits the synthesis of PCSK9 [216]. In a phase 1 trial in healthy volunteers with a LDL-cholesterol level >2.59

mmol/L (100 mg/dL), a single dose of inclisiran >100 mg lowered LDL-cholesterol levels by a mean of 50.6% from baseline with reductions maintained for up to 6 months in those who received doses >300 mg [217].

In a phase 2 multicentre study (ORION-1), 501 patients at high cardiovascular risk with elevated LDL-cholesterol levels received 2 doses of inclisiran (300 mg) at 0 and 90 days[218]. This regimen reduced LDL-cholesterol levels by 52.6 % with 48% of patients having an LDL-cholesterol concentration <0.04 mmol/L (1.5 mg/dL) at 180 days. Sustained reductions in apoB, non-HDL-cholesterol, VLDL-cholesterol and triglyceride levels as well as modest increases in HDL-cholesterol and apoA1 were also reported [219]. The magnitude of these changes are broadly comparable to those observed in trials of PCSK9-inhibiting monoclonal antibodies[219]. Although preliminary, these results raise the possibility of lowering cholesterol levels using twice yearly injections. This possibility is now being investigated in an extension study of ORION-1, which involves a head-to-head comparison between inclisiran 300 mg every 180 days and fortnightly evolucamab (ORION-3; NCT03060577). **[Au: Please add his study to the reference list.]**

[Au: Please add the trials mentioned in this paragraph to the reference list.] Ongoing trials are investigating the safety and efficacy of inclisiran in patients with familial hypercholesterolaemia (ORION-2; NCT02963311) and in patients with atherosclerotic cardiovascular disease (ORION-4). In addition, an open-label single dose study of 300 mg inclisiran is planned in 24 patients with renal impairment with a creatine clearance as low as 15 ml/min (ORION-7; NCT0315946).

[H2] CETP inhibitors

Cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters and triglycerides between mature HDLs and triglyceride-rich ApoB-containing lipoproteins and LDLs, thus modifying the lipid composition of HDLs (Figure 3)[31]. The first CETP inhibitor tested in humans, torcetrapib[121,220], increased HDL-cholesterol levels by 72% and decreased LDL-cholesterol levels by 25%. However, this **[Au: Please clarify what "this" refers to.]** was associated with an increased risk of cardiovascular events and mortality, probably through CETP-independent actions on blood pressure and circulating aldosterone and endothelin-1 levels[121,221].

The development of the CETP inhibitors evacetrapib and dalcetrapib was halted because of a lack of beneficial effects on cardiovascular events, despite improvement of the lipid profile (more than doubling of HDL-cholesterol level and 30% decrease in LDL-cholesterol level) **[Au: in which patient group?]** [31,123,222,223]. Another CETP inhibitor anacetrapib increased HDL-cholesterol by 138% and reduced LDL-cholesterol by 30% and Lp(a) by 39% in high risk patients on statin therapy[224]. The phase III Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL) trial in patients with pre-existing atherosclerotic vascular disease who were already on an effective LDL-cholesterol lowering regimen (mean LDL-cholesterol at randomization of 1.6 mmol/L (61 mg/dL)) showed a statistically significant decrease in major coronary events of 9% (HR 0.91 95% CI 0.85-0.97) in the inervenion group compared to placebo [225,226]. Unfortunately, patients with CKD and a serum creatinine level >200 μmol/L (>2.3 mg/dL) or with ESRD were excluded from this study. However, no benefit of anacetrapib was observed in patients with an eGFR <60 ml/min/1.73m^2 or macroalbuminuria, although the number of patients was small and there was no significant heterogeneity with respect to other groups.

Interestingly, the beneficial effects of anacetrapib seem to be the result of lowering non-HDL-cholesterol levels, rather than increasing HDL-cholesterol[223]. Anacetrapib is unlikely to become a licensed drug because the manufacturer has stopped development and a present will not be filing for approval. Clinical development of the CETP inhibitor obicetrapib was also halted in view of the REVEAL trial results, despite data from a phase II RCT showing that this agent increased HDL-cholesterol levels by >160% and decreased LDL-cholesterol levels by 47%[227].

These results of clinical trials with CETP inhibitors are perhaps not surprising. Some have suggested that the rise in HDL-cholesterol levels that is caused by administration of these agents is not solely due to enhanced reverse cholesterol transport. **[Au: Please reference this statement.]** Instead this effect is caused by blockade of the exchange of the cholesterol cargoes of HDL particles with the triglyceride cargo of IDL particles. This process is essential to transform oxidation-prone, pro-inflammatory and atherogenic IDL particles and triglyceride-rich LDL particles to cholesterol-ester rich LDL particles, which are removed from the circulation by liver LDL-receptors (Figure 1)[228,229].

[H2] Targeting lipoprotein(a)

Circulating levels of Lp(a) are fairly refractory to lifestyle and drug interventions, including statin therapy[230]. Only nicotinic acid, PCSK9 inhibitors and cetrapibs such as anacetrapib have been shown to lower Lp(a) levels by 15-25%, 15-30%, and 35-40%, respectively[31,231]. IONIS-APO(a) (previously called ISIS 681257) is an antisense oligonucleotide targeting the Lp(a) gene that was show to be safe and to decrease plasma Lp(a) levels by up to 80% in a phase I RCT[232]. Phase II RCTs with IONIS-APO(a) and IONIS-APO(a)-I, a ligand conjugated antisense oligonucleotide variant, have shown reductions in plasma Lp(a) of up to 96% **[Au: In which population?]** [233]. Currently no data are available on clinical outcomes using these agents.

[H2] Inhibitors of VLDL production

Inhibition of VLDL particle production decreases the levels of the downstream LDL particle[31]. Lomitapide inhibits microsomal triglyceride transfer protein (MTTP)[234], which assembles lipids with ApoB to form lipoproteins and mipomersen is an antisense agent that inhibits the synthesis of ApoB[235-237]. However, both agents may cause liver steatosis and are currently only in use as adjunct therapy in homozygous familial hypercholesterolemia[31,238-241]. No data are available on cardiovascular outcomes with either lomitapide or mipomersen[242,243].

[H2] ApoC-III antisense oligonucleotide

Increased levels of ApoC-III and the presence of ApoC-II in ApoB–conaining liposomes, ApoA-containing lipoproteins and Lp(a) are associated with increased atherogenic risk[244,245]. **[Au: What is the mechanism of this increased risk?]** An Apoprotein C-III gene antisense oligonucleotide, volanesorsen, has been shown to decreases serum triglyceride levels and **[Au: the incidence of?]** pancreatitis in patients with familial chylomicronemia syndrome[245,246]. Additional studies of volanesorsen are ongoing in patients with hypertriglyceridemia and other populations. **[Au: Please reference this statement.]**

[H2] Targeting angiopoietin-like protein 3

Angiopoietin-like proteins (ANGPTL) are important regulators of lipid metabolism[247] and ANGPTL3 is an endogenous inhibitor of LPL. Loss of function mutations of ANGPTL3 are associated with decreased LDL-cholesterol and triglyceride concentrations[247]. In healthy volunteers, the anti-ANGPTL3 antibody evinacumab reduced triglyceride levels by up to 76% and LDL-cholesterol by up to 23%[247] with similar reductions observed with the antisense oligonucleotide ANGPTL3-L_{Rx}, 63% and 33%, respectively[248].

[H2] HDL-peptide mimetics

HDL-peptide mimetics are parenteral drugs tha mimic the structural and functional properties of HDL precursors and stimulate reverse cholesterol transport[31]. In a phase 2B RCT, the plasma-derived ApoAI peptide CSL112 increased ApoA-I levels and *ex vivo* cholesterol efflux in patients who had experienced myocardial infarction in the week before enrollment but did not modify **[Au: the incidence of?]** major atherosclerotic events (a secondary end point)[249]. A study of CSL112 in patients with CKD stage 3 is ongoing (NCT02742103) **[Au: Please cite and include this trial in the reference list. If no data have been published a reference to the trial page at clinicaltrials.gov will be sufficient.]**.

CER-001 consists of recombinant human ApoA-I complexed with phospholipids that mimic HDL precursors[250]. A phase 2 RCT failed to show any effect of CER-001 on plaque regression in **[Au: 507?]** patients with post-acute coronary syndrome[251]. However, a subsequent analysis of the trial data by a second core laboratory did demonstrate reductions in total atheroma volume **[Au: in the intervention group compared wih the placebo group or compared to volume at enrollment?]**[252,253]. A repeat imaging trial is currently comparing the efficacy of high dose CER-001 versus placebo **[Au: in what population?]**[253].

[H1] Implications for health economics

In 2009, the healthcare costs associated with cardiovascular disease across the European Union was €106 billion, approximately 9% of the total health care outlay[79]. Most cost-effectiveness studies of cardiovascular disease prevention combine research data and simulation models[79,144,254-258] and estimates of cost-effectiveness can vary hugely depending on the assumptions made with regards to some basic parameters, especially the age and cardiovascular risk of the target population and the cost of the intervention[79]. Therefore, results for one condition or country will not necessarily be applicable to other situations. The incidence of serious adverse events can also have a major impact on cost-effectiveness[144] as can the availability of generic drugs[259].

Despite the adverse effects discussed above, the cost-effectiveness of statin therapy **[Au: for the prevention of cardiovascular events?]** in the general population is well established and the benefits persist in the long-term. **[Au: Please reference his statement.]** Moreover, for each year statin therapy is prolonged larger absolute benefits accrue[144]. In paients with CKD the evidence **[Au: for cost-effectiveness of statin therapy?]** is limited. However, studies from the

US and UK suggest comparable cost-effectiveness of statins for prevention of cardiovascular events **[Au: in the general population?]** and in patients with CKD not on dialysis[256,261].

Given the increased cardiovascular risk that is associated with CKD, the mollified effect of LDL-cholesterol reduction on cardiovascular events in patients with reduced renal function and the increased intolerance of high-dose statins **[Au: Do you mean increased incidence of adverse effects in patients with CKD? Please reference.]** treatment with novel lipid-modifying drugs might be an attractive option for physicians and their patients. Such a preference could be a matter of concern **[Au: for healthcare providers?]**, especially given the currently excessive costs of these new agents [262-264]. The issue of safety also needs to be addressed. The medical community as a whole, and the field of nephrology in particular, has previously fallen into the trap of extrapolating data from basic science, observational studies or clinical studies in other populations to justify treatments **[Au: in patients with CKD?]** that have eventually been shown to not be beneficial or even be damaging in later RCTs in this population [265-270].

[Au: Paragraph moved from the end of this section to improve flow. OK?] As any investment in a new therapy reduces the resources that are available for other therapies[278], lipid-modifying agents should be evaluated carefully for their health-economic impact as well as for their safety in patients with CKD[12]. In the past, patients with significant CKD **[Au: Please clarify what you mean by "significant CKD"?]** were routinely excluded from cardiovascular trials[279]. However, pressure should be put on regulatory and licensing authorities to demand the inclusion of patients with CKD in these trials in the future. Similar approaches together with several incentives have already improved the recruitment of women, children, elderly people and ethnic minorities into RCTs[280-282].

The importance of lifestyle modification, including adhering to a healthy diet, regular exercise, smoking cessation and maintaining a healthy weight is emphasized by many guidelines aimed at lowering cardiovascular risk in the general population, both before and after the use of lipid-lowering treatment[79,184,271-274]. However, such modifications remain an underexploited health-economic resource[12]. In Germany, societal costs from non-communicable diseases including CKD might decrease by €168 (£149; $207) billion per year if the population improves their dietary intake **[Au: Do you mean "reduces their dietary intake of salt, sugar and saturated fat"?]** to the recommended levels[275]. The idea of imposing a 'fat tax' or 'health' is controversial but might lead to a modification of dietary

habits [276] and decrease societal costs of non-communicable diseases [277]. In addition, the income raised by such a tax could be reinvested in health. Careful attention to health-economic aspects should become an essential aspect of medical and political decision-making, including regarding lipid-lowering in CKD [12].

[H1] The KDIGO Clinical Practice Guideline

The 2013 KDIGO Clinical Practice Guideline for Lipid Management[1] has caused extensive **[Au: Our journal style is to avoid use of "significantly" unless referring to statistical significance.]** discussion and controversy [283-285]. Similar to all KDIGO guidelines published to date, production of this guideline involved a thorough and rigorous process. Notably, the document makes recommendations for treatment but is not a rigid set of instructions. This point is especially important given that several of the recommendations were based on weak evidence. Although the summary recommendations can be interpreted as being very rigid, the guideline document puts these recommendations into context with plenty of room for personalization for individual patients. This context is especially important given that guidelines as a whole tend to be simplifications, which makes them easier to remember and implement but can result in the misclassification of individual patients[286,287]. In the 5 years since the publication of the KDIGO guideline, new clinical data has become available, novel therapies have emerged and other lipid management guidelines have been published. The KDIGO guideline deserves consideration and comment in the light of these developments (Table 3).

[H2] Assessment of lipid status

The KDIGO guideline recommends assessment of a lipid profile consisting of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides but does not recommend measurement of Lp(a), ApoB and other lipid markers[1]. As discussed above, emerging evidence suggests that these biomarkers might have utility in risk prediction and stratification in the general population and several subsequently published guidelines recommend their measurement[79,184]. However, their usefulness **[Au: for risk prediction or for diagnosis?]** in patients with CKD remains to be established.

Perhaps most controversially [283,284], the KDIGO guideline does not recommend follow-up measurement of lipid levels for the majority of patients. The evidence level for this statement is "not-graded" and the recommendation is based on the lack of data on treatment escalation to achieve specific LDL-cholesterol targets, substantial within person variability in LDL-

cholesterol measurements and the increased potential for medication toxicity in patients with CKD[288-290]. However, other reasons for follow-up measurements might exist, including monitoring or incentivizing adherence to treatment, which is known to be low in patients with CKD[291], change in renal replacement modality or concerns about the presence of new secondary causes of dyslipidaemia[1].

Other guidelines do suggest target cholesterol reductions[79,184]. The reasons for this difference are complex. Only taking into account evidence from RCTs ignores the totality of the available evidence so restricts the potential to prevent cardiovascular disease. Systematic reviews have repeatedly confirmed a dose-dependent reduction in cardiovascular events with lowering of LDL-cholesterol levels; that is, the greater the reduction in LDL-cholesterol, the greater the reduction in cardiovascular risk[143,145]. The benefits of reducing LDL-cholesterol do not seem to be restricted to statin treatment[292]. In addition, no level of LDL-cholesterol below which further reduction is not associated with benefit or results in harmful effects has ever been defined. Furthermore, considerable variability exists in the reduction in LDL-cholesterol levels that is achieved with therapy [293]. These factors support a tailored individualized approach to treatment with the setting of goals **[Au: Edit OK?]** to assist doctor–patient communication and potentially enhance adherence. Such an approach is particularly relevant to patients who are considered to be at very high cardiovascular risk, such as those with advanced CKD or ESRD, those who have recently experienced an acute cardiovascular event and those with genetic disorders of cholesterol metabolism and significant hypercholesterolaemia in whom statins are indicted.

[H2] Cholesterol-lowering treatment **[Au: I have reordered the text in this section to improve flow.]**

The KDIGO guideline recommends that patients with CKD stages 3-5 (not on dialysis) aged ≥50 years are treated with a statin or statin plus ezetimibe combination[1]. This recommendation is based on robust evidence and is consistent with other guidelines that do not recommend the use of risk assessment tools in this population. In adults with CKD stages 3-5 aged 18-49 years, KIDIGO recommends treatment if they have known coronary artery disease, diabetes mellitus, had a previous ischaemic stroke or an estimated 10-year incidence of coronary death or non-fatal myocardial infarction greater than 10%. Although the evidence for this recommendation is fairly weak, it is consistent with most other current guidelines (Table 4).

In contrast to the KDIGO guidelines, some guidelines advocate the use of lifetime-estimated risk of cardiovascular disease, rather than 10-year risk, to inform treatment decisions[294]. **[Au: Edit OK?]** The rationale is that estimates of 10-year risk might offer false reassurance over the longer term, especially in young patients who have a high lifetime risk[295]. This point might be particularly relevant for young patients with CKD in whom cardiovascular morbidity and mortality increase with age and deteriorating renal function. **[Au: Please reference this statement.]**

As statins and other cardioprotective drugs have become considerably less expensive and evidence of their long-term safety and efficacy has increased over time, considerable scope exists to extend their use beyond the traditional 10-year cardiovascular risk threshold. Furthermore, lipid levels change over time in response to certain treatments (such as immunosuppressive therapies), disease progression or remission and the development of malnutrition **[Au: Is he development of malnutrition particularly relevant for patients with ESRD?]**. Until concrete evidence exists regarding **[Au: statin use or use of lipid-lowering therapy in general?]** in patients with CKD, decisions on treatment are likely to continue to be based on acceptability, cost-effectiveness and practicality.

The KDIGO guideline also recommends treatment for patients with CKD stages 1-2 (eGFR >60 ml/min/1.73 m^2) aged >50 years who have pathological albuminuria (urinary albumin:creatinine ratio >30 mg/g). This recommendation is based on observational studies given the absence of RCTs specifically targeting this population. Although such treatment might be reasonable given the increased cardiovascular risk of these patients, the application of risk calculators as for the general population could equally be justified and would perhaps be more prudent. A CKD-cardiovascular disease model, incorporating albuminuria, has been developed as a resource for evaluating the health outcomes and cost-effectiveness of interventions in CKD [296]. However, this model is based on data from the SHARP trial and is only applicable to patients with CKD stage 3B or higher.

The KDIGO guideline does not specify an upper age limit **[Au: for lipid-lowering therapy?]**, whereas most guidelines recommend treating individuals aged >75 years only for secondary prevention. This difference is related to the lack of validated risk calculators for older individuals and their exclusion from many trials. Given the concerns regarding high-intensity statin usage in patients with CKD because of their increased polypharmacy and

comorbidity, a reasonable approach might be to tailor treatment in elderly individuals based on their individual preferences.

The KDIGO guideline focuses on cardiovascular risk to guide treatment and does not recommend treatment of any patient on the basis of a "high" cholesterol level *per se*. However, other guidelines such as the 2016 European Guidelines on cardiovascular risk prevention suggest lifestyle advice and possible drug treatment if LDL-cholesterol level is ≥4.9 mmol/L (≥ 190 mg/dL) even if the estimated 10-year cardiovascular risk is less than 1%. **[Au: Please reference this guideline.]** Furthermore this guideline suggests that most patients with a 10-year cardiovascular risk of 5–10% would benefit from lipid lowering therapy if baseline LDL-cholesterol is 2.6–4 mmol/L (100–155 mg/dL). This conclusion is based on the strong, robust and graded association between LDL-cholesterol levels and cardiovascular risk; the results of observational studies and trials of lipid lowering therapies using angiographic and clinical end-points; and the results of meta-analyses demonstrating a dose-dependent reduction of cardiovascular risk with LDL-cholesterol reduction [142-145,293]. These differing recommendations are relevant to the treatment of young patients with CKD and of patients on dialysis with subsantial hypercholesterolaemia who would not receive lipid lowering therapy based on the KDIGO guidelines. In these populations, tailoring of treatment based on patient preferences should perhaps be considered.

In patients receiving statins, KDIGO advises reducing the dose if eGFR is <60 ml/min/1.73 m^2, based on the reduced renal excretion of some statins, the increased polypharmacy and comorbidity **[Au: of patients with CKD]** and the doses of statins used in trials in CKD. This recommendation essentially means that high intensity statin therapy should be avoided. As moderate dose statin therapy is known to produce a mean reduction in LDL-cholesterol of 30%, **[Au: Please reference this statement.]** a substantial proportion of treated patients will not experience a reduction in LDL-cholesterol levels of this magnitude. This point is important in certain situations, including after an acute coronary syndrome. For example, the TNT trial found that a large group of patients with eGFRs of 45–59 ml/min/1.73 m^2 (CKD stage 3a) gained significant benefit from high dose atorvastatin therapy in terms of reduction of excess cardiovascular events[150]. Furthermore, the prescribing information for atorvastatin states that no dose adjustment is required for patients with CKD, whereas dose reduction for rosuvastatin is only required if the GFR is <30 ml/min/1.73m^2. Indeed, given that statins are now inexpensive (in stark contrast with the emerging lipid-lowering therapies) an argument could be made for adopting or studying an approach whereby stain-based regimens are chosen to

maximise the absolute reduction in LDL-cholesterol to achieve the largest treatment benefits in patients with CKD (rather than any target or goal-based approach). However, this approach is not necessarily without risk and may well need to be reserved for patients with high LDL-cholesterol levels. In addition to the intended inhibition of cholesterol production, statins inhibit the synthesis of byproducts of alternative (ie ubiquinone and dolichols) and intermediary (eg farnesyl-pyrophosphate and geranylgeranyl-pyrophosphates) pathways of mevalonate metabolism,[297,298] which have important functions including protein synthesis and transport, regulation of cell and tissue growth, mitochondrial function and gene transcription [299,300]. These unintended effects may result in serious adverse effects, including myopathy or rhabdomyolysis and hepatotoxicity, especially when statins are used at high doses in vulnerable patients with CKD or ESRD and low LDL-cholesterol levels[297,300].

The KDIGO guideline recommends that statins or combination therapy with a statin and ezetimibe should not be initiated in patients on dialysis [1]. However, they suggest that patients who are already receiving such therapy at the time of dialysis initiation should not discontinue. This recommendation is based on the SHARP trial in which 2,141 patients with CKD progressed to needing dialysis during the study period but were analysed in the non-dialysis group in which overall benefit was observed[156]. These two recommendations seem rather incongruous and somewhat difficult to reconcile with the remaining KDIGO guidance. They partly reflect the very limited RCT evidence available rather than the totality of evidence.

One possible explanation for why a patient on dialysis might benefit from statin-based treatment only if they were receiving this therapy before dialysis initiation relates to the duration of treatment and/or exposure to risk. Although all RCTs of cholesterol-lowering therapies in patients on dialysis have been conducted over a period of around 5-years, the period of exposure to risk in the study participants is much longer with the atherosclerotic process having started years or decades earlier. As such, the 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidaemia[274] suggest initiating treatment in paiens on dialysis if they are likely to eiher remain on dialysis for many years or receive a transplant. Indeed, this suggestion seems to align with the KDIGO recommendation of treating all adult kidney transplant recipients with a statin. It also appears to be particularly relevant for diabetic patients on dialysis with high LDL-cholesterol levels (>3.76 mmol/L; >145 mg/dL)[155].

[H1] Conclusions

Patients with all stages of CKD including those with ESRD on dialysis and kidney transplant recipients remain at high cardiovascular risk. Despite this risk, patients with CKD have repeatedly been shown to be less likely **[Au: than patients without CKD?]** to receive statin therapy for primary or secondary prevention of cardiovascular events[301]. In this context of under-treatment, the 2013 KDIGO guideline for lipid management provides pragmatic guidance for lipid-lowering treatment. However, some of the KDIGO recommendations, especially for situations with a poor evidence base, can be considered too restrictive when compared to other guidelines aimed at the general population **[Au: Edit OK?]**.

Starting lipid-lowering therapy, especially in patients with no previous cardiovascular event, can be a complex process. Shared decision making is especially important when the risks and costs of an intervention are immediate and the benefits are in the future. Two patients may choose different strategies and both are right based on their preferences. As a rule, clinicians should help to inform choices but avoid dictating treatments. Similarly, the role of guidelines is to inform choices but not to dictate them, especially in areas where the evidence is weak.

Several novel therapies to manage dyslipidaemia are in clinical development. To be useful for patients with CKD, these agents must be safe, effective, available and of proven benefit in clinical trials in this population. Many of the novel treatments are bio-drugs **[Au: biologics?]** that are very expensive to produce. Thus, even if these agents are proven to be safe and effective, as well as being readily available, the high manufacturing costs may make them unaffordable so restrict their widespread use. The very real challenge for physicians managing patients with CKD and ESRD is to ensure that we get the evidence to support or refute the use of next generation lipid-lowering agents in this population without having to rely on extrapolation from studies in the general population. We must avoid, as has too often happened in the past, the widespread use of expensive and unproven treatments that later turn out to be unsafe or ineffective. The responsibility for this **[Au: do you mean "for ensuring safety and efficacy"?]** rests largely with manufacturers and regulatory authorities. However, as health-care professionals we too must push for, conduct and commit to large RCTs to answer these important questions. Importantly, all physicians looking after patients with CKD or ESRD must enroll **[Au: those who are willing to participate?]** into RCTs if we are to deliver the best possible care with the resources available.

Acknowledgements

AO was supported by Spanish Government ISCIII FEDER funds (PI16/02057, ISCIII-RETIC REDinREN RD16/0009) and Community of Madrid (B2017/BMD-3686 CIFRA2-CM).

Author contributions

C.J.F., P.B.M., M.K., R.V., and A.O. researched the data, made substantial contributions to discussions of the content, wrote the article and reviewed or edited the manuscript before submission. C.Z. researched the data, made substantial contributions to discussions of the content and wrote the article. P.S., G.H.H., P.R., Z.A.M., F.M., J.M.V., J.M., R.E., M.C.V. and G.M.L made substantial contributions to discussion of the content and reviewed or edited the manuscript before submission. **[Au: Statement OK?]**

Competing interests

AO is a consultant for Sanofi Genzyme and has received speaker fees from Amgen. **[Au: Please confirm that the other authors declare no competing interests.]**

[Au: Please use your software to update the reference list.]

1. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Working Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl* **3**, 263-305 (2013).
2. Hohenstein, B. Lipoprotein(a) in nephrological patients. *Clin Res Cardiol Suppl* **12**, 27-30 (2017).
3. Heine, G.H., Rogacev, K.S., Weingartner, O. & Marsche, G. Still a reasonable goal: Targeting cholesterol in dialysis and advanced chronic kidney disease patients. *Semin Dial* **30**, 390-394 (2017).
4. Go, A.S., Chertow, G.M., Fan, D., McCulloch, C.E. & Hsu, C.Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* **351**, 1296-1305 (2004).
5. Matsushita, K*., et al.* Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* **375**, 2073-2081 (2010).
6. Vanholder, R*., et al.* Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* **20**, 1048-1056 (2005).
7. U.S. Renal Data System. USRDS 2015 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethseda, MD. (2015).
8. de Jager, D.J*., et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* **302**, 1782-1789 (2009).
9. Steenkamp, R., Rao, A. & Roderick, P. UK Renal Registry 17th Annual Report: Chapter 5 Survival and Cause of Death in UK Adult Patients on Renal Replacement Therapy in 2013: National and Centre-specific Analyses. *Nephron* **129 Suppl 1**, 99-129 (2015).
10. Bottomley, M.J. & Harden, P.N. Update on the long-term complications of renal transplantation. *Br Med Bull* **106**, 117-134 (2013).

11. Neale, J. & Smith, A.C. Cardiovascular risk factors following renal transplant. *World J Transplant* **5**, 183-195 (2015).
12. Vanholder, R.*, et al.* Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. *Nat Rev Nephrol* **13**, 393-409 (2017).
13. Jardine, A.G., Gaston, R.S., Fellstrom, B.C. & Holdaas, H. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet* **378**, 1419-1427 (2011).
14. Hart, A., Weir, M.R. & Kasiske, B.L. Cardiovascular risk assessment in kidney transplantation. *Kidney Int* **87**, 527-534 (2015).
15. Pilmore, H., Dent, H., Chang, S., McDonald, S.P. & Chadban, S.J. Reduction in cardiovascular death after kidney transplantation. *Transplantation* **89**, 851-857 (2010).
16. Hager, M.R., Narla, A.D. & Tannock, L.R. Dyslipidemia in patients with chronic kidney disease. *Rev Endocr Metab Disord* **18**, 29-40 (2017).
17. Zheng-Lin, B. & Ortiz, A. Lipid Management in Chronic Kidney Disease: Systematic Review of PCSK9 Targeting. *Drugs* **78**, 215-229 (2018).
18. Visconti, L.*, et al.* Lipid disorders in patients with renal failure: Role in cardiovascular events and progression of chronic kidney disease. *J Clin Translational Endocrinol* **6**, 8-14 (2016).
19. Florens, N., Calzada, C., Lyasko, E., Juillard, L. & Soulage, C.O. Modified Lipids and Lipoproteins in Chronic Kidney Disease: A New Class of Uremic Toxins. *Toxins (Basel)* **8**, 1-27 (2016).
20. Deighan, C.J., Caslake, M.J., McConnell, M., Boulton-Jones, J.M. & Packard, C.J. The atherogenic lipoprotein phenotype: small dense LDL and lipoprotein remnants in nephrotic range proteinuria. *Atherosclerosis* **157**, 211-220 (2001).
21. Vaziri, N.D., Sato, T. & Liang, K. Molecular mechanisms of altered cholesterol metabolism in rats with spontaneous focal glomerulosclerosis. *Kidney Int* **63**, 1756-1763 (2003).
22. Mesquita, J., Varela, A. & Medina, J.L. Dyslipidemia in renal disease: causes, consequences and treatment. *Endocrinol Nutr* **57**, 440-448 (2010).
23. Kaysen, G.A. New insights into lipid metabolism in chronic kidney disease. *J Ren Nutr* **21**, 120-123 (2011).
24. Reiss, A.B., Voloshyna, I., De Leon, J., Miyawaki, N. & Mattana, J. Cholesterol Metabolism in CKD. *Am J Kidney Dis* **66**, 1071-1082 (2015).
25. Vaziri, N.D. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol* **290**, F262-272 (2006).
26. Kronenberg, F. HDL in CKD-The Devil Is in the Detail. *J Am Soc Nephrol* **29**, 1356-1371 (2018).
27. Annema, W. & von Eckardstein, A. Dysfunctional high-density lipoproteins in coronary heart disease: implications for diagnostics and therapy. *Transl Res* **173**, 30-57 (2016).
28. Julve, J., Martin-Campos, J.M., Escola-Gil, J.C. & Blanco-Vaca, F. Chylomicrons: Advances in biology, pathology, laboratory testing, and therapeutics. *Clin Chim Acta* **455**, 134-148 (2016).
29. Kaysen, G.A. Lipid and lipoprotein metabolism in chronic kidney disease. *J Ren Nutr* **19**, 73-77 (2009).
30. Tsimihodimos, V., Mitrogianni, Z. & Elisaf, M. Dyslipidemia associated with chronic kidney disease. *Open Cardiovasc Med J* **5**, 41-48 (2011).
31. Gaudet, D., Drouin-Chartier, J.P. & Couture, P. Lipid Metabolism and Emerging Targets for Lipid-Lowering Therapy. *Can J Cardiol* **33**(2017).

32. Bermudez-Lopez, M.*, et al.* New perspectives on CKD-induced dyslipidemia. *Expert Opin Ther Targets* **21**, 967-976 (2017).
33. Visconti, L.*, et al.* Lipid disorders in patients with renal failure: Role in cardiovascular events and progression of chronic kidney disease. *J Clin Translational Endocrinol* **6**, 8-14 (2016).
34. Kwan, B.C., Kronenberg, F., Beddhu, S. & Cheung, A.K. Lipoprotein metabolism and lipid management in chronic kidney disease. *J Am Soc Nephrol* **18**, 1246-1261 (2007).
35. Chen, H.*, et al.* Combined Clinical Phenotype and Lipidomic Analysis Reveals the Impact of Chronic Kidney Disease on Lipid Metabolism. *J Proteome Res* **16**, 1566-1578 (2017).
36. Chu, M., Wang, A.Y., Chan, I.H., Chui, S.H. & Lam, C.W. Serum small-dense LDL abnormalities in chronic renal disease patients. *Br J Biomed Sci* **69**, 99-102 (2012).
37. Chait, A., Brazg, R.L., Tribble, D.L. & Krauss, R.M. Susceptibility of small, dense, low-density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B. *Am J Med* **94**, 350-356 (1993).
38. Gardner, C.D., Fortmann, S.P. & Krauss, R.M. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* **276**, 875-881 (1996).
39. Kwiterovich, P.O., Jr. Lipoprotein heterogeneity: diagnostic and therapeutic implications. *Am J Cardiol* **90**, 1i-10i (2002).
40. Gelissen, I.C.*, et al.* ABCA1 and ABCG1 synergize to mediate cholesterol export to apoA-I. *Arterioscler Thromb Vasc Biol* **26**, 534-540 (2006).
41. Voloshyna, I. & Reiss, A.B. The ABC transporters in lipid flux and atherosclerosis. *Prog Lipid Res* **50**, 213-224 (2011).
42. Cardinal, H., Raymond, M.A., Hebert, M.J. & Madore, F. Uraemic plasma decreases the expression of ABCA1, ABCG1 and cell-cycle genes in human coronary arterial endothelial cells. *Nephrol Dial Transplant* **22**, 409-416 (2007).
43. Guarnieri, G.F.*, et al.* Lecithin-cholesterol acyltransferase (LCAT) activity in chronic uremia. *Kidney Int Suppl*, S26-30 (1978).
44. Attman, P.O., Alaupovic, P. & Gustafson, A. Serum apolipoprotein profile of patients with chronic renal failure. *Kidney Int* **32**, 368-375 (1987).
45. Vaziri, N.D., Liang, K. & Parks, J.S. Down-regulation of hepatic lecithin:cholesterol acyltransferase gene expression in chronic renal failure. *Kidney Int* **59**, 2192-2196 (2001).
46. Barter, P.J.*, et al.* Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* **23**, 160-167 (2003).
47. Kimura, H.*, et al.* Hepatic lipase mutation may reduce vascular disease prevalence in hemodialysis patients with high CETP levels. *Kidney Int* **64**, 1829-1837 (2003).
48. Beddhu, S., Kimmel, P.L., Ramkumar, N. & Cheung, A.K. Associations of metabolic syndrome with inflammation in CKD: results From the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* **46**, 577-586 (2005).
49. Seiler, S.*, et al.* Cholesteryl ester transfer protein activity and cardiovascular events in patients with chronic kidney disease stage V. *Nephrol Dial Transplant* **23**, 3599-3604 (2008).
50. Navab, M.*, et al.* Oxidized lipids as mediators of coronary heart disease. *Curr Opin Lipidol* **13**, 363-372 (2002).
51. Yamamoto, S.*, et al.* Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. *J Am Coll Cardiol* **60**, 2372-2379 (2012).

52. Shroff, R.*, et al.* HDL in children with CKD promotes endothelial dysfunction and an abnormal vascular phenotype. *J Am Soc Nephrol* **25**, 2658-2668 (2014).
53. Thompson, M.*, et al.* Kidney Function as a Determinant of HDL and Triglyceride Concentrations in the Australian Population. *J Clin Med* **5**(2016).
54. Batista, M.C.*, et al.* Apolipoprotein A-I, B-100, and B-48 metabolism in subjects with chronic kidney disease, obesity, and the metabolic syndrome. *Metabolism* **53**, 1255-1261 (2004).
55. Cheung, A.K., Parker, C.J., Ren, K. & Iverius, P.H. Increased lipase inhibition in uremia: identification of pre-beta-HDL as a major inhibitor in normal and uremic plasma. *Kidney Int* **49**, 1360-1371 (1996).
56. Ginsberg, H.N.*, et al.* Apolipoprotein B metabolism in subjects with deficiency of apolipoproteins CIII and AI. Evidence that apolipoprotein CIII inhibits catabolism of triglyceride-rich lipoproteins by lipoprotein lipase in vivo. *J Clin Invest* **78**, 1287-1295 (1986).
57. Mead, J.R., Irvine, S.A. & Ramji, D.P. Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med (Berl)* **80**, 753-769 (2002).
58. Liang, K., Oveisi, F. & Vaziri, N.D. Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. *Kidney Int* **53**, 626-630 (1998).
59. Liang, K. & Vaziri, N.D. Acquired VLDL receptor deficiency in experimental nephrosis. *Kidney Int* **51**, 1761-1765 (1997).
60. Vaziri, N.D. & Liang, K. Down-regulation of VLDL receptor expression in chronic experimental renal failure. *Kidney Int* **51**, 913-919 (1997).
61. Li, P.K.*, et al.* Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J Am Soc Nephrol* **24**, 1889-1900 (2013).
62. Barbagallo, C.M.*, et al.* Heparin induces an accumulation of atherogenic lipoproteins during hemodialysis in normolipidemic end-stage renal disease patients. *Hemodial Int* **19**, 360-367 (2015).
63. Bugeja, A.L. & Chan, C.T. Improvement in lipid profile by nocturnal hemodialysis in patients with end-stage renal disease. *ASAIO J* **50**, 328-331 (2004).
64. Nordestgaard, B.G. & Varbo, A. Triglycerides and cardiovascular disease. *Lancet* **384**, 626-635 (2014).
65. Triglyceride Coronary Disease Genetics, C.*, et al.* Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* **375**, 1634-1639 (2010).
66. Lamprea-Montealegre, J.A.*, et al.* Chronic kidney disease, plasma lipoproteins, and coronary artery calcium incidence: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* **33**, 652-658 (2013).
67. Lamprea-Montealegre, J.A.*, et al.* CKD, plasma lipids, and common carotid intima-media thickness: results from the multi-ethnic study of atherosclerosis. *Clin J Am Soc Nephrol* **7**, 1777-1785 (2012).
68. Lamprea-Montealegre, J.A.*, et al.* Coronary heart disease risk associated with the dyslipidemia of chronic kidney disease. *Heart* (In press).
69. Postorino, M., Marino, C., Tripepi, G., Zoccali, C. & Group, C.W. Abdominal obesity modifies the risk of hypertriglyceridemia for all-cause and cardiovascular mortality in hemodialysis patients. *Kidney Int* **79**, 765-772 (2011).
70. van Capelleveen, J.C., van der Valk, F.M. & Stroes, E.S. Current therapies for lowering lipoprotein (a). *J Lipid Res* **57**, 1612-1618 (2016).
71. Berg, K. A New Serum Type System in Man--the Lp System. *Acta Pathol Microbiol Scand* **59**, 369-382 (1963).

72. Clarke, R.*, et al.* Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* **361**, 2518-2528 (2009).
73. Emerging Risk Factors, C.*, et al.* Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* **302**, 412-423 (2009).
74. Thanassoulis, G.*, et al.* Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* **368**, 503-512 (2013).
75. Langsted, A., Kamstrup, P.R. & Nordestgaard, B.G. Lipoprotein(a): fasting and nonfasting levels, inflammation, and cardiovascular risk. *Atherosclerosis* **234**, 95-101 (2014).
76. Kamstrup, P.R., Tybjaerg-Hansen, A. & Nordestgaard, B.G. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* **63**, 470-477 (2014).
77. Zewinger, S.*, et al.* Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study. *Lancet Diabetes Endocrinol* **5**, 534-543 (2017).
78. Bajaj, A.*, et al.* Lipoprotein(a) and Risk of Myocardial Infarction and Death in Chronic Kidney Disease: Findings From the CRIC Study (Chronic Renal Insufficiency Cohort). *Arterioscler Thromb Vasc Biol* **37**, 1971-1978 (2017).
79. Catapano, A.L.*, et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J* **37**, 2999-3058 (2016).
80. Agrawal, S., Zaritsky, J.J., Fornoni, A. & Smoyer, W.E. Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. *Nat Rev Nephrol* **14**, 57-70 (2018).
81. Vaziri, N.D. Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney Int* **90**, 41-52 (2016).
82. Dounousi, E.*, et al.* Oxidative stress is progressively enhanced with advancing stages of CKD. *Am J Kidney Dis* **48**, 752-760 (2006).
83. Garcia-Cruset, S., Carpenter, K.L., Guardiola, F., Stein, B.K. & Mitchinson, M.J. Oxysterol profiles of normal human arteries, fatty streaks and advanced lesions. *Free Radic Res* **35**, 31-41 (2001).
84. Lizard, G.*, et al.* Characterization and comparison of the mode of cell death, apoptosis versus necrosis, induced by 7beta-hydroxycholesterol and 7-ketocholesterol in the cells of the vascular wall. *Arterioscler Thromb Vasc Biol* **19**, 1190-1200 (1999).
85. Uchida, K. Role of reactive aldehyde in cardiovascular diseases. *Free Radic Biol Med* **28**, 1685-1696 (2000).
86. Palinski, W.*, et al.* ApoE-deficient mice are a model of lipoprotein oxidation in atherogenesis. Demonstration of oxidation-specific epitopes in lesions and high titers of autoantibodies to malondialdehyde-lysine in serum. *Arterioscler Thromb* **14**, 605-616 (1994).
87. Levitan, I., Volkov, S. & Subbaiah, P.V. Oxidized LDL: diversity, patterns of recognition, and pathophysiology. *Antioxid Redox Signal* **13**, 39-75 (2010).
88. Drozdz, D.*, et al.* Oxidative Stress Biomarkers and Left Ventricular Hypertrophy in Children with Chronic Kidney Disease. *Oxid Med Cell Longev* **2016**, 7520231 (2016).
89. Reis, A.*, et al.* Top-down lipidomics of low density lipoprotein reveal altered lipid profiles in advanced chronic kidney disease. *J Lipid Res* **56**, 413-422 (2015).
90. Massy, Z.A. & de Zeeuw, D. LDL cholesterol in CKD--to treat or not to treat? *Kidney Int* **84**, 451-456 (2013).

91. Speer, T.*, et al.* Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2. *Immunity* **38**, 754-768 (2013).
92. Vaziri, N.D. HDL abnormalities in nephrotic syndrome and chronic kidney disease. *Nat Rev Nephrol* **12**, 37-47 (2016).
93. Haas, M.E.*, et al.* The Role of Proprotein Convertase Subtilisin/Kexin Type 9 in Nephrotic Syndrome-Associated Hypercholesterolemia. *Circulation* **134**, 61-72 (2016).
94. Rogacev, K.S.*, et al.* PCSK9 Plasma Concentrations Are Independent of GFR and Do Not Predict Cardiovascular Events in Patients with Decreased GFR. *PLoS One* **11**, e0146920 (2016).
95. Agarwal, A. & Prasad, G.V. Post-transplant dyslipidemia: Mechanisms, diagnosis and management. *World J Transplant* **6**, 125-134 (2016).
96. de Groen, P.C. Cyclosporine, low-density lipoprotein, and cholesterol. *Mayo Clin Proc* **63**, 1012-1021 (1988).
97. Princen, H.M., Meijer, P., Wolthers, B.G., Vonk, R.J. & Kuipers, F. Cyclosporin A blocks bile acid synthesis in cultured hepatocytes by specific inhibition of chenodeoxycholic acid synthesis. *Biochem J* **275 (Pt 2)**, 501-505 (1991).
98. Kramer, B.K.*, et al.* Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. *Nephrol Dial Transplant* **20**, 968-973 (2005).
99. White, M.*, et al.* Conversion from cyclosporine microemulsion to tacrolimus-based immunoprophylaxis improves cholesterol profile in heart transplant recipients with treated but persistent dyslipidemia: the Canadian multicentre randomized trial of tacrolimus vs cyclosporine microemulsion. *J Heart Lung Transplant* **24**, 798-809 (2005).
100. Alghamdi, S., Nabi, Z., Skolnik, E., Alkorbi, L. & Albaqumi, M. Cyclosporine versus tacrolimus maintenance therapy in renal transplant. *Exp Clin Transplant* **9**, 170-174 (2011).
101. Massy, Z.A.*, et al.* Hyperlipidaemia and post-heparin lipase activities in renal transplant recipients treated with sirolimus or cyclosporin A. *Nephrol Dial Transplant* **15**, 928 (2000).
102. Morrisett, J.D.*, et al.* Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. *J Lipid Res* **43**, 1170-1180 (2002).
103. Kasiske, B.L.*, et al.* Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. *Am J Transplant* **8**, 1384-1392 (2008).
104. Emerging Risk Factors, C.*, et al.* Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* **302**, 1993-2000 (2009).
105. Lowrie, E.G. & Lew, N.L. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* **15**, 458-482 (1990).
106. Baigent, C., Landray, M.J. & Wheeler, D.C. Misleading associations between cholesterol and vascular outcomes in dialysis patients: the need for randomized trials. *Semin Dial* **20**, 498-503 (2007).
107. Baigent, C., Burbury, K. & Wheeler, D. Premature cardiovascular disease in chronic renal failure. *Lancet* **356**, 147-152 (2000).
108. Zoccali, C. Cardiovascular risk in uraemic patients-is it fully explained by classical risk factors? *Nephrol Dial Transplant* **15**, 454-457 (2000).
109. Storey, B.C.*, et al.* Lowering LDL cholesterol reduces cardiovascular risk independently of presence of inflammation. *Kidney Int* **93**, 1000-1007 (2018).

110. Saran, R.*, et al.* US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* **69**, S465-S480 (2017).
111. Methven, S., Steenkamp, R. & Fraser, S. UK Renal Registry 19th Annual Report: Chapter 5 Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2015: National and Centre-specific Analyses. *Nephron* **137 Suppl 1**, 117-150 (2017).
112. Cholesterol Treatment Trialists Collaboration*, et al.* Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol* **4**, 829-839 (2016).
113. Chue, C.D., Townend, J.N., Steeds, R.P. & Ferro, C.J. Arterial stiffness in chronic kidney disease: causes and consequences. *Heart* **96**, 817-823 (2010).
114. Moody, W.E., Edwards, N.C., Chue, C.D., Ferro, C.J. & Townend, J.N. Arterial disease in chronic kidney disease. *Heart* (2012).
115. Edwards, N.C.*, et al.* Defining the Natural History of Uremic Cardiomyopathy in Chronic Kidney Disease: The Role of Cardiovascular Magnetic Resonance. *JACC Cardiovasc Imaging* **7**, 703-714 (2014).
116. Mall, G., Huther, W., Schneider, J., Lundin, P. & Ritz, E. Diffuse intermyocardiocytic fibrosis in uraemic patients. *Nephrol Dial Transplant* **5**, 39-44 (1990).
117. Aoki, J.*, et al.* Clinical and pathologic characteristics of dilated cardiomyopathy in hemodialysis patients. *Kidney Int* **67**, 333-340 (2005).
118. Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B. & Dawber, T.R. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* **62**, 707-714 (1977).
119. Arntzenius, A.C.*, et al.* Diet, lipoproteins, and the progression of coronary atherosclerosis. The Leiden Intervention Trial. *N Engl J Med* **312**, 805-811 (1985).
120. Castelli, W.P.*, et al.* Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* **256**, 2835-2838 (1986).
121. Barter, P.J.*, et al.* Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* **357**, 2109-2122 (2007).
122. Investigators, A.-H.*, et al.* Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* **365**, 2255-2267 (2011).
123. Schwartz, G.G.*, et al.* Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* **367**, 2089-2099 (2012).
124. Group, H.T.C.*, et al.* Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* **371**, 203-212 (2014).
125. Lo, J.C., Go, A.S., Chandra, M., Fan, D. & Kaysen, G.A. GFR, body mass index, and low high-density lipoprotein concentration in adults with and without CKD. *Am J Kidney Dis* **50**, 552-558 (2007).
126. Ganda, A.*, et al.* Mild renal dysfunction and metabolites tied to low HDL cholesterol are associated with monocytosis and atherosclerosis. *Circulation* **127**, 988-996 (2013).
127. Anderson, J.L.*, et al.* High density lipoprotein (HDL) particles from end-stage renal disease patients are defective in promoting reverse cholesterol transport. *Sci Rep* **7**, 41481 (2017).
128. Zewinger, S.*, et al.* HDL cholesterol is not associated with lower mortality in patients with kidney dysfunction. *J Am Soc Nephrol* **25**, 1073-1082 (2014).
129. Silbernagel, G.*, et al.* HDL cholesterol, apolipoproteins, and cardiovascular risk in hemodialysis patients. *J Am Soc Nephrol* **26**, 484-492 (2015).

130. Moradi, H., *et al.* Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients. *Nephrol Dial Transplant* **29**, 1554-1562 (2014).
131. Moradi, H., *et al.* Association of serum lipids with outcomes in Hispanic hemodialysis patients of the West versus East Coasts of the United States. *Am J Nephrol* **41**, 284-295 (2015).
132. Chang, T.I., *et al.* Inverse Association Between Serum Non-High-Density Lipoprotein Cholesterol Levels and Mortality in Patients Undergoing Incident Hemodialysis. *J Am Heart Assoc* **7**(2018).
133. Sarwar, N., *et al.* Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* **115**, 450-458 (2007).
134. Levy, R.I. & Glueck, C.J. Hypertriglyceridemia, diabetes mellitus, and coronary vessel disease. *Arch Intern Med* **123**, 220-228 (1969).
135. Shoji, T., Nishizawa, Y., Nishitani, H., Yamakawa, M. & Morii, H. Roles of hypoalbuminemia and lipoprotein lipase on hyperlipoproteinemia in continuous ambulatory peritoneal dialysis. *Metabolism* **40**, 1002-1008 (1991).
136. Vaziri, N.D. Causes of dysregulation of lipid metabolism in chronic renal failure. *Semin Dial* **22**, 644-651 (2009).
137. Zammit, A.R., Katz, M.J., Derby, C., Bitzer, M. & Lipton, R.B. Chronic Kidney Disease in Non-Diabetic Older Adults: Associated Roles of the Metabolic Syndrome, Inflammation, and Insulin Resistance. *PLoS One* **10**, e0139369 (2015).
138. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383-1389 (1994).
139. Sacks, F.M., *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* **335**, 1001-1009 (1996).
140. Colhoun, H.M., *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**, 685-696 (2004).
141. Collins, R., *et al.* MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* **361**, 2005-2016 (2003).
142. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **376**, 1670-1681 (2010).
143. Cholesterol Treatment Trialists, C., *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* **385**, 1397-1405 (2015).
144. Collins, R., *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* **388**, 2532-2561 (2016).
145. Cholesterol Treatment Trialists, C., *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581-590 (2012).
146. Shepherd, J., *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* **333**, 1301-1307 (1995).
147. Ridker, P.M., *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* **359**, 2195-2207 (2008).

148. Tonelli, M.*, et al.* Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* **110**, 1557-1563 (2004).
149. Ridker, P.M., MacFadyen, J., Cressman, M. & Glynn, R.J. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol* **55**, 1266-1273 (2010).
150. Shepherd, J.*, et al.* Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol* **51**, 1448-1454 (2008).
151. Holdaas, H.*, et al.* Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* **361**, 2024-2031 (2003).
152. Holdaas, H.*, et al.* Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant* **5**, 2929-2936 (2005).
153. Fellstrom, B.C.*, et al.* Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* **360**, 1395-1407 (2009).
154. Wanner, C.*, et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* **353**, 238-248 (2005).
155. Marz, W.*, et al.* Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. *Clin J Am Soc Nephrol* **6**, 1316-1325 (2011).
156. Baigent, C.*, et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* **377**, 2181-2192 (2011).
157. De Nicola, L.*, et al.* Prognostic role of LDL cholesterol in non-dialysis chronic kidney disease: Multicenter prospective study in Italy. *Nutr Metab Cardiovasc Dis* **25**, 756-762 (2015).
158. Haynes, R.*, et al.* Effects of lowering LDL cholesterol on progression of kidney disease. *J Am Soc Nephrol* **25**, 1825-1833 (2014).
159. Su, X.*, et al.* Effect of Statins on Kidney Disease Outcomes: A Systematic Review and Meta-analysis. *Am J Kidney Dis* **67**, 881-892 (2016).
160. Tonelli, M.*, et al.* Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* **24**, 979-986 (2013).
161. Tsimikas, S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol* **69**, 692-711 (2017).
162. Hopewell, J.C., Haynes, R. & Baigent, C. The Role of Lipoprotein(a) in Chronic Kidney Disease. *J Lipid Res* **59**, 577-585 (2018).
163. Krane, V.*, et al.* Long-term effects following 4 years of randomized treatment with atorvastatin in patients with type 2 diabetes mellitus on hemodialysis. *Kidney Int* **89**, 1380-1387 (2016).
164. Palmer, S.C.*, et al.* HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* **5**, CD007784 (2014).
165. Palmer, S.C.*, et al.* HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev*, CD004289 (2013).
166. Palmer, S.C.*, et al.* HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev* **1**, CD005019 (2014).

167. Major, R.W., Cheung, C.K., Gray, L.J. & Brunskill, N.J. Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis. *Clin J Am Soc Nephrol* **10**, 732-739 (2015).
168. Green, D., Ritchie, J.P. & Kalra, P.A. Meta-analysis of lipid-lowering therapy in maintenance dialysis patients. *Nephron Clin Pract* **124**, 209-217 (2013).
169. Hou, W.*, et al.* Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J* **34**, 1807-1817 (2013).
170. Libby, P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* **32**, 2045-2051 (2012).
171. McCausland, F.R.*, et al.* C-Reactive Protein and Risk of ESRD: Results From the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT). *Am J Kidney Dis* **68**, 873-881 (2016).
172. Oesterle, A., Laufs, U. & Liao, J.K. Pleiotropic Effects of Statins on the Cardiovascular System. *Circ Res* **120**, 229-243 (2017).
173. Ridker, P.M.*, et al.* Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet* **373**, 1175-1182 (2009).
174. Ridker, P.M.*, et al.* Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* **377**, 1119-1131 (2017).
175. Ridker, P.M.*, et al.* Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* **391**, 319-328 (2018).
176. Everett, B.M.*, et al.* Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. *Am Heart J* **166**, 199-207 e115 (2013).
177. Handelman, G.J.*, et al.* Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. *Kidney Int* **59**, 1960-1966 (2001).
178. Gupta, J.*, et al.* Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin J Am Soc Nephrol* **7**, 1938-1946 (2012).
179. Akchurin, O.M. & Kaskel, F. Update on inflammation in chronic kidney disease. *Blood Purif* **39**, 84-92 (2015).
180. Amdur, R.L.*, et al.* Inflammation and Progression of CKD: The CRIC Study. *Clin J Am Soc Nephrol* **11**, 1546-1556 (2016).
181. Rubins, H.B.*, et al.* Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* **341**, 410-418 (1999).
182. Frick, M.H.*, et al.* Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* **317**, 1237-1245 (1987).
183. Robins, S.J.*, et al.* Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* **285**, 1585-1591 (2001).
184. Jellinger, P.S.*, et al.* American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidaemia and prevention of cardiovascular disease. *Endocrine Practice* **23**, 1-87 (2017).

185. Broeders, N., Knoop, C., Antoine, M., Tielemans, C. & Abramowicz, D. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? *Nephrol Dial Transplant* **15**, 1993-1999 (2000).
186. Lipscombe, J., Lewis, G.F., Cattran, D. & Bargman, J.M. Deterioration in renal function associated with fibrate therapy. *Clin Nephrol* **55**, 39-44 (2001).
187. Lipscombe, J. & Bargman, J.M. Fibrate-induced increase in blood urea and creatinine. *Nephrol Dial Transplant* **16**, 1515 (2001).
188. Sica, D.A. Fibrate therapy and renal function. *Curr Atheroscler Rep* **11**, 338-342 (2009).
189. Markossian, T.*, et al.* Controversies Regarding Lipid Management and Statin Use for Cardiovascular Risk Reduction in Patients With CKD. *Am J Kidney Dis* **67**, 965-977 (2016).
190. Lloyd-Jones, D.M.*, et al.* 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol* **70**, 1785-1822 (2017).
191. Koskinas, K.C.*, et al.* Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J* **39**, 1172-1180 (2018).
192. Barter, P.J. & Rye, K.A. New Era of Lipid-Lowering Drugs. *Pharmacol Rev* **68**, 458-475 (2016).
193. Seidah, N.G.*, et al.* The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc Natl Acad Sci U S A* **100**, 928-933 (2003).
194. Abifadel, M.*, et al.* Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* **34**, 154-156 (2003).
195. Cohen, J.*, et al.* Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nat Genet* **37**, 161-165 (2005).
196. Horton, J.D., Cohen, J.C. & Hobbs, H.H. Molecular biology of PCSK9: its role in LDL metabolism. *Trends Biochem Sci* **32**, 71-77 (2007).
197. Benn, M., Nordestgaard, B.G., Grande, P., Schnohr, P. & Tybjaerg-Hansen, A. PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses. *J Am Coll Cardiol* **55**, 2833-2842 (2010).
198. Cohen, J.C., Boerwinkle, E., Mosley, T.H., Jr. & Hobbs, H.H. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* **354**, 1264-1272 (2006).
199. Marais, D.A., Blom, D.J., Petrides, F., Goueffic, Y. & Lambert, G. Proprotein convertase subtilisin/kexin type 9 inhibition. *Curr Opin Lipidol* **23**, 511-517 (2012).
200. Lambert, G., Sjouke, B., Choque, B., Kastelein, J.J. & Hovingh, G.K. The PCSK9 decade. *J Lipid Res* **53**, 2515-2524 (2012).
201. Lepor, N.E. & Kereiakes, D.J. The PCSK9 Inhibitors: A Novel Therapeutic Target Enters Clinical Practice. *Am Health Drug Benefits* **8**, 483-489 (2015).
202. Stein, E.A. & Raal, F. Reduction of low-density lipoprotein cholesterol by monoclonal antibody inhibition of PCSK9. *Annu Rev Med* **65**, 417-431 (2014).
203. Toth, P.P.*, et al.* Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease. *Kidney Int* **93**, 1397-1408 (2018).
204. Robinson, J.G.*, et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* **372**, 1489-1499 (2015).

205. Steg, P., Kumbhani, D.J. & Eagle, K.A. Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - ODYSSEY OUTCOMES. http://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes (2018).
206. Robinson, J.G., *et al.* Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA* **311**, 1870-1882 (2014).
207. Koren, M.J., *et al.* Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol* **63**, 2531-2540 (2014).
208. Stroes, E., *et al.* Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* **63**, 2541-2548 (2014).
209. Blom, D.J., *et al.* A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* **370**, 1809-1819 (2014).
210. Raal, F.J., *et al.* PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet* **385**, 331-340 (2015).
211. Nicholls, S.J., *et al.* Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA* **316**, 2373-2384 (2016).
212. Sabatine, M.S., *et al.* Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* **376**, 1713-1722 (2017).
213. Sabatine, M.S., *et al.* Rationale and design of the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial. *Am Heart J* **173**, 94-101 (2016).
214. Ballantyne, C.M., *et al.* Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomized, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. *Am J Cardiol* **115**, 1212-1221 (2015).
215. Elbashir, S.M., *et al.* Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *Nature* **411**, 494-498 (2001).
216. Khvorova, A. Oligonucleotide Therapeutics - A New Class of Cholesterol-Lowering Drugs. *N Engl J Med* **376**, 4-7 (2017).
217. Fitzgerald, K., *et al.* A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. *N Engl J Med* **376**, 41-51 (2017).
218. Ray, K.K., *et al.* Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. *N Engl J Med* **376**, 1430-1440 (2017).
219. Ray, K.K., *et al.* Effect of an siRNA Therapeutic Targeting PCSK9 on Atherogenic Lipoproteins: Pre-Specified Secondary End Points in ORION 1. *Circulation* (2018).
220. Brousseau, M.E., *et al.* Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. *N Engl J Med* **350**, 1505-1515 (2004).
221. Forrest, M.J., *et al.* Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. *Br J Pharmacol* **154**, 1465-1473 (2008).
222. Lincoff, A.M., *et al.* Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* **376**, 1933-1942 (2017).
223. Tall, A.R. & Rader, D.J. The Trials and Tribulations of CETP Inhibitors. *Circ Res* **122**, 106-112 (2018).

224. Cannon, C.P.*, et al.* Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* **363**, 2406-2415 (2010).
225. Reveal Collaborative, G.*, et al.* Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)-A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: Trial design, recruitment, and baseline characteristics. *Am Heart J* **187**, 182-190 (2017).
226. Group, H.T.R.C. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N Engl J Med* **377**, 1217-1227 (2017).
227. Hovingh, G.K.*, et al.* Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* **386**, 452-460 (2015).
228. Vaziri, N.D. Role of dyslipidemia in impairment of energy metabolism, oxidative stress, inflammation and cardiovascular disease in chronic kidney disease. *Clin Exp Nephrol* **18**, 265-268 (2014).
229. Moradi, H. & Vaziri, N.D. Molecular mechanisms of disorders of lipid metabolism in chronic kidney disease. *Front Biosci (Landmark Ed)* **23**, 146-161 (2018).
230. Feinberg, M.W. No small task: therapeutic targeting of Lp(a) for cardiovascular disease. *Lancet* **388**, 2211-2212 (2016).
231. Thomas, T.*, et al.* CETP (Cholesteryl Ester Transfer Protein) Inhibition With Anacetrapib Decreases Production of Lipoprotein(a) in Mildly Hypercholesterolemic Subjects. *Arterioscler Thromb Vasc Biol* **37**, 1770-1775 (2017).
232. Tsimikas, S.*, et al.* Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* **386**, 1472-1483 (2015).
233. Viney, N.J.*, et al.* Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* **388**, 2239-2253 (2016).
234. Hussain, M.M., Rava, P., Walsh, M., Rana, M. & Iqbal, J. Multiple functions of microsomal triglyceride transfer protein. *Nutr Metab (Lond)* **9**, 14 (2012).
235. Raal, F.J.*, et al.* Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet* **375**, 998-1006 (2010).
236. Yamamoto, T., Wada, F. & Harada-Shiba, M. Development of Antisense Drugs for Dyslipidemia. *J Atheroscler Thromb* **23**, 1011-1025 (2016).
237. Panta, R., Dahal, K. & Kunwar, S. Efficacy and safety of mipomersen in treatment of dyslipidemia: a meta-analysis of randomized controlled trials. *J Clin Lipidol* **9**, 217-225 (2015).
238. Samaha, F.F., McKenney, J., Bloedon, L.T., Sasiela, W.J. & Rader, D.J. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. *Nat Clin Pract Cardiovasc Med* **5**, 497-505 (2008).
239. Hussain, M.M. & Bakillah, A. New approaches to target microsomal triglyceride transfer protein. *Curr Opin Lipidol* **19**, 572-578 (2008).
240. Cuchel, M.*, et al.* Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet* **381**, 40-46 (2013).
241. Vuorio, A., Tikkanen, M.J. & Kovanen, P.T. Inhibition of hepatic microsomal triglyceride transfer protein - a novel therapeutic option for treatment of

homozygous familial hypercholesterolemia. *Vasc Health Risk Manag* **10**, 263-270 (2014).
242. Zodda, D., Giammona, R. & Schifilliti, S. Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. *Pharmacy (Basel)* **6**, E10 (2018).
243. Ajufo, E. & Rader, D.J. New Therapeutic Approaches for Familial Hypercholesterolemia. *Annu Rev Med* **69**, 113-131 (2018).
244. Gordts, P.L.*, et al.* ApoC-III inhibits clearance of triglyceride-rich lipoproteins through LDL family receptors. *J Clin Invest* **126**, 2855-2866 (2016).
245. Pechlaner, R.*, et al.* Very-Low-Density Lipoprotein-Associated Apolipoproteins Predict Cardiovascular Events and Are Lowered by Inhibition of APOC-III. *J Am Coll Cardiol* **69**, 789-800 (2017).
246. Yang, X.*, et al.* Reduction in lipoprotein-associated apoC-III levels following volanesorsen therapy: phase 2 randomized trial results. *J Lipid Res* **57**, 706-713 (2016).
247. Dewey, F.E.*, et al.* Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. *N Engl J Med* **377**, 211-221 (2017).
248. Graham, M.J.*, et al.* Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. *N Engl J Med* **377**, 222-232 (2017).
249. Michael Gibson, C.*, et al.* Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Apolipoprotein A-I, After Acute Myocardial Infarction: The AEGIS-I Trial (ApoA-I Event Reducing in Ischemic Syndromes I). *Circulation* **134**, 1918-1930 (2016).
250. Tardy, C.*, et al.* CER-001, a HDL-mimetic, stimulates the reverse lipid transport and atherosclerosis regression in high cholesterol diet-fed LDL-receptor deficient mice. *Atherosclerosis* **232**, 110-118 (2014).
251. Tardif, J.C.*, et al.* Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. *Eur Heart J* **35**, 3277-3286 (2014).
252. Kataoka, Y.*, et al.* Regression of coronary atherosclerosis with infusions of the high-density lipoprotein mimetic CER-001 in patients with more extensive plaque burden. *Cardiovasc Diagn Ther* **7**, 252-263 (2017).
253. Di Bartolo, B.A., Schwarz, N., Andrews, J. & Nicholls, S.J. Infusional high-density lipoproteins therapies as a novel strategy for treating atherosclerosis. *Arch Med Sci* **13**, 210-214 (2017).
254. Ward, S.*, et al.* A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* **11**, 1-160, iii-iv (2007).
255. Mistry, H.*, et al.* Cost-effectiveness of a European preventive cardiology programme in primary care: a Markov modelling approach. *BMJ Open* **2**, e001029 (2012).
256. Erickson, K.F.*, et al.* Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. *J Am Coll Cardiol* **61**, 1250-1258 (2013).
257. McConnachie, A.*, et al.* Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* **35**, 290-298 (2014).
258. Stam-Slob, M.C., van der Graaf, Y., Greving, J.P., Dorresteijn, J.A. & Visseren, F.L. Cost-Effectiveness of Intensifying Lipid-Lowering Therapy With Statins Based on Individual Absolute Benefit in Coronary Artery Disease Patients. *J Am Heart Assoc* **6**, e004648 (2017).

259. Rubio-Sans, P. The cost effectiveness of statin therapies in Spain in 2010, after the introduction of generics and reference prices. *Am J Cardiovasc Drugs* **10**, 369-382 (2010).
260. Krumholz, H.M. Statins evidence: when answers also raise questions. *Bmj* **354**, i4963 (2016).
261. Mihaylova, B.*, et al.* Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP). *Am J Kidney Dis* **67**, 576-584 (2016).
262. National Institute for Health and Care Excellence. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. *Technology Appraisal Guidance* **Published: 22nd June 2016**, nice.org.uk/guidance/ta394 (2016).
263. Villa, G.*, et al.* Cost-effectiveness of Evolocumab in Patients With High Cardiovascular Risk in Spain. *Clin Ther* **39**, 771-786 e773 (2017).
264. Gandra, S.R.*, et al.* Cost-Effectiveness of LDL-C Lowering With Evolocumab in Patients With High Cardiovascular Risk in the United States. *Clin Cardiol* **39**, 313-320 (2016).
265. Pratt, C.M. & Moye, L.A. The cardiac arrhythmia suppression trial. Casting suppression in a different light. *Circulation* **91**, 245-247 (1995).
266. Besarab, A.*, et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* **339**, 584-590 (1998).
267. Carlberg, B., Samuelsson, O. & Lindholm, L.H. Atenolol in hypertension: is it a wise choice? *Lancet* **364**, 1684-1689 (2004).
268. Singh, A.K.*, et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* **355**, 2085-2098 (2006).
269. Pfeffer, M.A.*, et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* **361**, 2019-2032 (2009).
270. Investigators, A.*, et al.* Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* **361**, 1953-1962 (2009).
271. Stone, N.J.*, et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* **63**, 2889-2934 (2014).
272. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification: Guideline 181. https://www.nice.org.uk/guidance/cg181 (2014).
273. Authors/Task Force, M.*, et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* **252**, 207-274 (2016).
274. Anderson, T.J.*, et al.* 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol* **32**, 1263-1282 (2016).
275. Meier, T.*, et al.* Healthcare Costs Associated with an Adequate Intake of Sugars, Salt and Saturated Fat in Germany: A Health Econometrical Analysis. *PLoS One* **10**, e0135990 (2015).
276. Smed, S., Scarborough, P., Rayner, M. & Jensen, J.D. The effects of the Danish saturated fat tax on food and nutrient intake and modelled health outcomes: an

econometric and comparative risk assessment evaluation. *Eur J Clin Nutr* **70**, 681-686 (2016).
277. Smith-Spangler, C.M., Juusola, J.L., Enns, E.A., Owens, D.K. & Garber, A.M. Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. *Ann Intern Med* **152**, 481-487, W170-483 (2010).
278. Barrett, A., Roques, T., Small, M. & Smith, R.D. How much will Herceptin really cost? *Bmj* **333**, 1118-1120 (2006).
279. Ng, K.P., Townend, J.N. & Ferro, C.J. Randomised-controlled trials in chronic kidney disease--a call to arms! *Int J Clin Pract* **66**, 913-915 (2012).
280. Joseph, P.D., Craig, J.C. & Caldwell, P.H. Clinical trials in children. *Br J Clin Pharmacol* **79**, 357-369 (2015).
281. Liu, K.A. & Mager, N.A. Women's involvement in clinical trials: historical perspective and future implications. *Pharm Pract (Granada)* **14**, 708 (2016).
282. Downing, N.S.*, et al.* Participation of the elderly, women, and minorities in pivotal trials supporting 2011-2013 U.S. Food and Drug Administration approvals. *Trials* **17**, 199 (2016).
283. Palmer, S.C., Strippoli, G.F. & Craig, J.C. KHA-CARI commentary on the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. *Nephrology (Carlton)* **19**, 663-666 (2014).
284. Sarnak, M.J.*, et al.* KDOQI US commentary on the 2013 KDIGO Clinical Practice Guideline for Lipid Management in CKD. *Am J Kidney Dis* **65**, 354-366 (2015).
285. Schneider, M.P.*, et al.* Implementation of the KDIGO guideline on lipid management requires a substantial increase in statin prescription rates. *Kidney Int* **88**, 1411-1418 (2015).
286. Eddy, D.M.*, et al.* Individualized guidelines: the potential for increasing quality and reducing costs. *Ann Intern Med* **154**, 627-634 (2011).
287. Cooper, R.A. & Straus, D.J. Clinical guidelines, the politics of value, and the practice of medicine: physicians at the crossroads. *J Oncol Pract* **8**, 233-235 (2012).
288. Glasziou, P.P.*, et al.* Monitoring cholesterol levels: measurement error or true change? *Ann Intern Med* **148**, 656-661 (2008).
289. Takahashi, O.*, et al.* Lipid re-screening: what is the best measure and interval? *Heart* **96**, 448-452 (2010).
290. Hayward, R.A. & Krumholz, H.M. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. *Circ Cardiovasc Qual Outcomes* **5**, 2-5 (2012).
291. Chang, T.I., Desai, M., Solomon, D.H. & Winkelmayer, W.C. Kidney function and long-term medication adherence after myocardial infarction in the elderly. *Clin J Am Soc Nephrol* **6**, 864-869 (2011).
292. Cannon, C.P.*, et al.* Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* **372**, 2387-2397 (2015).
293. Boekholdt, S.M.*, et al.* Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* **64**, 485-494 (2014).
294. J. B. S. Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* **100 Suppl 2**, ii1-ii67 (2014).
295. Marma, A.K., Berry, J.D., Ning, H., Persell, S.D. & Lloyd-Jones, D.M. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes* **3**, 8-14 (2010).

296. Schlackow, I.*, et al.* A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease. *Heart* **103**, 1880-1890 (2017).
297. Epstein, M. & Vaziri, N.D. Statins in the management of dyslipidemia associated with chronic kidney disease. *Nat Rev Nephrol* **8**, 214-223 (2012).
298. Vaziri, N.D. & Norris, K.C. Reasons for the lack of salutary effects of cholesterol-lowering interventions in end-stage renal disease populations. *Blood Purif* **35**, 31-36 (2013).
299. Massy, Z.A.*, et al.* Importance of geranylgeranyl pyrophosphate for mesangial cell DNA synthesis. *Kidney Int Suppl* **71**, S80-83 (1999).
300. Beltowski, J., Wojcicka, G. & Jamroz-Wisniewska, A. Adverse effects of statins - mechanisms and consequences. *Curr Drug Saf* **4**, 209-228 (2009).
301. Ezekowitz, J.*, et al.* The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. *J Am Coll Cardiol* **44**, 1587-1592 (2004).
302. Burke, A.C. & Huff, M.W. ATP-citrate lyase: genetics, molecular biology and therapeutic target for dyslipidemia. *Curr Opin Lipidol* **28**, 193-200 (2017).
303. Stein, E., Bays, H., Koren, M., Bakker-Arkema, R. & Bisgaier, C. Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. *J Clin Lipidol* **10**, 1212-1222 (2016).
304. Meyers, C.D.*, et al.* Effect of the DGAT1 inhibitor pradigastat on triglyceride and apoB48 levels in patients with familial chylomicronemia syndrome. *Lipids Health Dis* **14**, 8 (2015).
305. U. S. Preventive Services Task Force*, et al.* Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* **316**, 1997-2007 (2016).
306. Chou, R., Dana, T., Blazina, I., Daeges, M. & Jeanne, T.L. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* **316**, 2008-2024 (2016).

Key points

- An independent, graded inverse relationship exists between cardiovascular risk and estimated glomerular filtration rate; patients with end-stage renal disease (ESRD) are at extremely high risk of cardiovascular events
- In chronic kidney disease (CKD) and ESRD, dysregulation of lipid metabolism results in increased levels of triglycerides and oxidised lipoproteins and reduced levels of high-density lipoprotein cholesterol; low-density lipoprotein cholesterol levels are usually normal
- As eGFR declines, there is a trend towards smaller relative risk reductions for major vascular events with statin-based therapy with little evidence of benefit in patients on dialysis

- Deteriorating renal function results in a unique cardiovascular phenotype with an increasing proportion of cardiovascular deaths due to heart failure and arrhythmias, rather than due to atherosclerotic events
- Several novel therapies are being developed to treat dyslipidaemias and their associated risks; most of these agents are biologics, which are very expensive to produce
- Currently there is very little evidence to support the use of novel lipid-lowering agents in patients with CKD or ESRD; however a need exists for further studies of these therapies

[Au: I suggest that we cut Box 1 as your Review is already very long with 8 display items and the box is not necessary to aid understanding of the article. If you feel strongly that the box should be included please shorten the text to fit our limit of 300 words and cite it in the text. Alternatively the box could be included in supplementary information.]

Figure 1. Derangements in lipoprotein metabolism in chronic kidney disease. **[Au: Edited title ok?]** In the endogenous pathway, the liver secretes triglyceride-rich VLDL particles that transport triglycerides to peripheral tissues. As triglycerides are hydrolysed by LPL, the VLDL particles decrease in size to become IDL particles and finally LDL particles, which retain considerable amounts of cholesterol. The LDL particles transport cholesterol to the liver and peripheral tissues and are cleared by the LDL receptor, as well as by other specific receptors and scavenger receptors. In the exogenous pathway, triglyceride-rich chylomicrons transport dietary lipids absorbed from the gut. Chylomicrons are catabolised by LPL, resulting in the generation of free fatty acids that are taken up by liver, muscle and adipose tissue. Chylomicrons rapidly diminish in size to become chylomicron remnants that are taken up by the liver via the LDL receptor. HDL particles have a key role in the process of reverse cholesterol transport, which transports cholesterol from peripheral cells **[Au: such**

as macrophages and endothelial cells?] to the liver. As renal function declines, a gradual quantitative shift towards a uraemic lipid profile occurs. **[Au: Please provide some more detail of the changes that characterize this profile?]**The lipid profile is also further modified by co-morbidities including diabetes mellitus and nephrotic syndrome. In parallel to the quantitative changes, major qualitative changes in the lipoprotein particles that render them more atherogenic also occur, including increased oxidation. ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ApoA-I, apolipoprotein A-I; ApoA-IV; CETP, cholesteryl ester transfer protein; IDL, intermediate-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; LDL-R, LDL receptor; LPL, lipoprotein lipase; LRP; SR-B1, scavenger receptor B1; VLDL, very low-density lipoprotein. **[Au: Please define c-LDL]**

Figure 2 Role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in cholesterol transport. a | LDL particles bind to LDL-receptors (LDL-R) on the surface of cells to form a complex that is taken up by the cell. As pH decreases inside the endosome **[Au:OK?]**, the LDL-receptor dissociates from this complex. LDL-cholesterol is incorporated into the cell and the LDL-receptor recycles to the cell surface. **b** | PCSK9 is an extracellular protein that binds directly to the LDL-receptor and induces its internalization and degradation. Therapeutic agents that target PCSK9 either reduce the synthesis of the protein or block its binding to the LDL-receptor. These agents prevent degradation of the LDL-receptor so preserve LDL-receptor recycling, which increases LDL-receptor density on the hepatocyte surface so enables more LDL-cholesterol to be removed from the circulation. LDL, low density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; VLDL, very low density lipoprotein.

Figure 3 | Role of cholesteryl ester transfer protein (CETP) in cholesterol transport.

HDL particles are initially cholesterol-free lipoproteins that are synthesized in hepatocytes and enterocytes. Extrahepatic tissues remove excess cholesterol by transferring it as free cholesterol to HDL particles. This free cholesterol is then either sent to the liver directly in a process dependent on hepatic scavenger receptor B1 (SR-B1) or indirectly via conversion into cholesteryl esters by LCAT. Cholesteryl esters are transported to the liver either by a direct but minor pathway that is dependent on SR-B1 or via an indirect major pathway that involves transfer to VLDL and LDL particles by CETP. Cholesterol ester is then taken up by the liver from these particles via the LDL receptor (LDL-R). Inhibition of CETP increases HDL-cholesterol levels and decreases the amount of cholesterol in atherogenic ApoB-containing VLDL and LDL particles. CETP, Cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase; LDL-R, low density lipoprotein-receptor.

[Au: I suggest that we cut figure 4 as it is not original and it does not add value to your Review. The meta-analysis is cited and interested readers can refer to the original paper if they want more details on the results.]

Table 1 | Lipid Profiles associated with CKD, dialysis and nephrotic syndrome.

[Au: Ref 34 was published in 2007 so this data is quite old. Please update the table with recent data and references if possible. We will look into obtaining permissions to adapt the table but if we are not able to obtain these we will have to cut it from the Review.]

Parameter	CKD stage 1-5	Nephrotic Syndrome	Haemodialysis	Peritoneal dialysis
Total cholesterol	⇗	⇧⇧	⇔⇧	⇧
LDL-cholesterol	⇗	⇧⇧	⇔⇧	⇧
HDL-cholesterol	⇩	⇩	⇩	⇩
Non-HDL-cholesterol*	⇗	⇧⇧	⇔⇧	⇧
Triglycerides	⇗	⇧⇧	⇧	⇧
Lp(a)	⇧	⇧⇧	⇧	⇧⇧

Normal (⇔), increased (⇧), markedly increased (⇧⇧), and decreased (⇩) plasma levels compared with patients with normal renal function; increasing (⇗) plasma levels with

decreasing glomerular filtration rate. *Non-HDL-cholesterol includes cholesterol in low-density lipoprotein, very low-density lipoprotein, intermediate-density lipoprotein and chylomicrons and their remnants. Adapted from Kwan CH et al [34]

Table 2 | Emerging lipid-modifying therapies [Au: I have reformatted this table to fit our journal style and page layout (portrait orientation). ATP citrate lyase inhibitors, acetylcoenzyme A carboxylase inhibitors and diacylglycerol acyltransferase 1 inhibitors do not seem to be discussed in the main text. Please check if these should be included/discussed.]

Target	Drug family	Mechanism [Au: Please check if my edits are correct.]	Individual drugs	Status	Results [Au: In this column when more than one drug is listed please specify which result is for which drug.]	Ref(s)
PCSK9	PCSK9 inhibitors	Increase the clearance of LDL particles	Alirocumab, evolocumab, bococizumab.	[Au: Which drugs?] available for FH Development of Bococizumab halted	[Au: Which drug(s)?] reduced the risk of major cardiovascular events in high-risk individuals and in patients with FH	204, 210,214
	PCSK9 siRNA	Increase the clearance of LDL particles	Inclisiran	Phase II RCT completed	Lowered LDL-cholesterol levels [Au: in which population?]	216
ATP citrate lyase	ATP citrate lyase inhibitor	Reduces the synthesis of LDL particles	Bempedoic acid	Phase II RCT completed	Lowered LDL-cholesterol and C-reactive protein levels [Au: in which population]	302
CETP	CETP inhibitors	Inhibit the exchange of cholesteryl esters and triglycerides between HDL and TG-rich lipoproteins	Torcetrapib Evaccetrapib Dalcetrapib Anacetrapib Obicetrapib.	Phase III RCT [Au: of which drugs?] completed Clinical development [Au: of which drug?] halted	[Au: Which drugs?] Increased HDL and decreased LDL cholesterol levels [Au: in which population] Lower atherosclerotic events with Anacetrapib [Au: in which population?]	121,222,123,225,227
ApoA-I	ApoA-I mimic peptides	[Au: Increase or decrease?] the cholesterol efflux capacity of HDL particles	CSL112 CER-001	Phase II RCTs completed Phase III RCT announced for CSL112	Conflicting results on atheroma regression [Au: With which drug? In patients with post-acute coronary syndrome?]	249,252
Lp(a) [Au: changed from Apo(a) OK?]	Lp(a) antisense oligonucleotide	[Au: Inhibition of?] Lp(a) synthesis	IONIS-APO(a)	Phase II RCTs completed	Lowers plasma Lp(a) >90% [Au: in which population]	233
MTTP	MTTP inhibitor	Inhibition of VLDL particle production	Lomitapide	Available for FH	>50% reduction in LDL-cholesterol [Au: in which population]	234
ApoB	ApoB antisense oligonucleotide	Inhibition of ApoB synthesis	Mipomersen	Available for FH	>50% reduction in LDL-cholesterol [Au: in which population]	235
ANGPTL3	Anti-ANGPTL3 antibody	[Au: inhibits?] VLDL particle secretion	Evinacumab	Phase II RCT completed Phase III RCT ongoing	Lower triglycerides (76%) and LDL-cholesterol (23%) [Au: in which population]	247
	ANGPTL3 antisense oligonucleotide	[Au: inhibits?] VLDL particle secretion	ANGPTL3-L_{Rx}	Phase I/II RCT completed	Lower triglycerides (63%) and LDL-cholesterol (33%) [Au: in which population]	248
Acetylcoenzyme A carboxylase	Acetylcoenzyme A carboxylase inhibitor	Enhances the clearance of VLDL particles	Gemcabene	Phase II RCT completed Phase III RCT planned	Lower LDL-cholesterol, and C-reactive protein levels [Au: in which population?]	303
ApoC-III	ApoC-III antisense oligonucleotide	Triglyceride-rich ApoC-III-lipoproteins [Au: What is the effect on these	Volanesorsen	Phase III RCT completed Filed for Federal Drug Administration approval	Lowers triglyceride levels in patients with familial chylomicronemia [Au:OK?]	245

		lipoproteins – what specifically is targeted?]				
Diacylglycerol acyltransferase 1	Diacylglycerol acyltransferase 1 inhibitor	Reduces triglyceride synthesis **[Au: in chylomicrons?]**	Pradigastat	Phase III RCT terminated	Lower triglycerides (70%) **[Au: in which population]**.	[304]

ANGPTL3, angiopoietin-like 3; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; CETP, cholesteryl ester transfer protein; CKD, chronic kidney disease; FH, familial hypercholesterolaemia; HDL, high density lipoprotein; LDL, low density lipoprotein; LDL-Lp (a), lipoprotein (a); MTTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin-kexin type 9; RCT, randomised controlled trial; sCr, serum creatinine; siRNA, small interfering RNA; VLDL, very low density lipoprotein.

Table 3 | Suggested areas for revision of the KDIGO Clinical Practice Guideline for lipid management in CKD[1]. [Au: Edited title OK? We have a limit of 98 characters including spaces.]

KDIGO Recommendation	Potential revision
Assessment of lipid status	
In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (1C)	Consideration might be given to other emerging markers of dyslipidaemia (e.g. lipoprotein(a), Apolipoprotein B), although these should mostly be reserved for research studies
In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients. (Not Graded)	Consider follow-up measurement in certain circumstances, for example in response to changes in clinical status and/or medications, in situations where intensive lipid lowering is potentially beneficial and to reinforce adherence
Pharmacological cholesterol-lowering treatment	
In adults aged ≥50 years with eGFR<60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), we recommend treatment with a statin or statin/ezetimibe combination. In adults aged ≥50 years with CKD and GFR>60 ml/min/1.73 m^2 (GFR categories G1-G2) we recommend treatment with a statin. In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following: • known coronary disease (myocardial infarction or coronary revascularization) • diabetes mellitus • prior ischemic stroke • estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10% In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued In adult kidney transplant recipients, we suggest treatment with a statin	Consideration needs to be given to patients with progressive CKD, especially if high levels of proteinuria are present Potential consideration also needs to be given to patients with high estimated life-time risk likely to progress to dialysis and transplantation. In individuals with known coronary disease, secondary prevention recommendations may apply, including LDL-cholesterol targets Consider decision to be individualised if patient is expected to have a long renal career, receive a kidney transplant or has high LDL cholesterol levels
Triglyceride-lowering treatment	
In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised	**[Au: NA?]**

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; **[Au: NA, not applicable.]**

Table 4 | Summary of guidelines for lipid-modification [Au: Should this be lipid-lowering therapy?] therapy for the management of dyspipidaemia

Society (year)	Recommendations	Assessment of risk for primary prevention	Patients with CKD or ESRD [Au: I've merged this coulumn with the other notes column OK?]	Ref
KDIGO (2013) [Au: Please complete to enable easy comparisons]				[1]
American College of Cardiology/American Heart Association (2013)	Different statin intensity depending on 10-year ACSVD risk and presence of other risk factors	10-year risk of ACSVD using the pooled cohorts equation	No recommendation for patients on dialysis or those with severe heart failure	[271]
Joint British Societies (2014)	Target non-HDL-cholesterol <2.5mmol/L and LDL-cholesterol <1.8 mmol/L	JBS-3 risk calculator, to assess 10-year and life-time CVD risk	No risk estimation required for CKD stages 3-5 No mention of patients on dialysis except an indirect reference to KDIGO guidelines	[294]
Cardiovascular disease: risk assessment and reduction, including lipid modification (2014; updated 2016)	Low, medium, high intensity statin treatment depending on risk for primary prevention High intensity (atorvastatin 80 mg) for secondary prevention.	10-year CVD event risk using the QRISK2 assessment tool.	Risk assessment not required if GFR <60 ml/min/1.73 m^2 or albuminuria (level not defined) Offer atorvastatin 20 mg to patients with CKD for the primary or secondary prevention of CVD Aim for >40% reduction in non-HDL-cholesterol and consider increasing dose if this target is not achieved. No reference to patients on dialysis or transplant recipients	[272]
European Atherosclerosis Society/European Society of Cardiology (2016)	Target LDL-cholesterol <1.8 mmol/L in very high risk, <2.6 in high risk and <3.0 in low to intermediate risk patients	10-year risk of first fatal cardiovascular event using SCORE system	Patients with CKD are considered to be at high or very high cardiovascular risk Have broadly accepted KDIGO recommendations	[79]
Sixth Taskforce European Society of Cardiology and other societies (2016)	Target LDL-cholesterol <1.8 mmol/L in very high risk, <2.6 in high risk and <3.0 in low to intermediate risk patients	10-year risk of first fatal CV event using SCORE system	Patients with CKD are considered to be at high or very high cardiovascular risk Have broadly accepted KDIGO recommendations	[273]
US Preventative Services Task Force (2016)	All offered low-to moderate dose statins Primary prevention recommended for adults aged <75 years only [Au:OK?]	10-year risk of CVD using the ACC/AHA pooled cohorts equation	No recommendations provided [Au:OK?]	[305,306]
Canadian Cardiovascular Society (2016)	Target > 50% LDL-cholesterol reduction	10-year Framingham Heart Study Risk Score modified for family history or CV age using Cardiovascular Life Expectancy Model (CLEM)	Risk assessment not required if GFR <60 ml/min/1.73 m^2or ACR > 3.0 mg/mmol Suggest not initiating lipid lowering treatment in patients on dialysis Treatment might be desireable in younger individuals and in those who might become eligible for kidney Otherwise broadly similar to KDIGO.	[274]
American Society of Endocrinologists 2017)	Treatment goals for LDL-cholesterol should be personalized to levels of risk low <130 mg/dL, moderate & high <100 mg/dL, very high <70 mg/dL, extreme < 55 mg/dL	10-year risk of a coronary event using either Framingham Risk Assessment Tool, MESA, Reynolds Risk Score, UKPDS risk engine	Patients with CKD stages 4-5 are classified as high, very high or extreme risk depending on the presence of other risk factors	[184]

Conventional to SI units conversion: LDL-cholesterol: mg/dl to mmol/L conversion factor 0.0259. ACR: mg/g to mg/mmol conversion factor 0.113